UTS UNIVERSITY OF TECHNOLOGY SYDNEY

PharmaBlock - A Reliable and Intelligent Platform for Pharmaceutical Data Analytics

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Certificate of Original Authorship

I declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Computer Science/Faculty of Engineering and Information Technology at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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بسم الله الرحمن الرحيم

In the name of Allah, most gracious and most merciful

وَقُل رَّبِّ زِدْنِي عِلْمًا

(O my Lord, increase me in knowledge.)

(Al-Quran 20:114)

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Publications

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Abstract

Recently, blockchain technology was introduced to the public to provide a secure environment that is an immutable, consensus-based and transparent system in the finance technology world. However, blockchain is also being applied to other fields where trust and transparency are needed. The need for the reliable sharing of pharmaceutical information between various stakeholders is essential. The usage of blockchain technology adds traceability and visibility to supply chains such as pharmaceutical supply chains and provides all information from end to end. Currently, data is either stored and managed by large manufacturers and pharmacy retailers using their own centralized system. Several existing approaches and methods that allow pharmaceutical information to be stored and shared between the healthcare provider and other stakeholders in a centralized manner have been discussed in the literature. These methods are not very useful in terms of data utility. Blockchain technology offers a distributed framework that can positively affect the process of assembling and sharing pharmaceutical information between the relevant stakeholders, such as the U.S Food and Drugs Administration (FDA) [1], manufacturers, distributors, pharmacy retailers and researchers.

In this research, we propose the *PharmaBlock* blockchain framework as the base of the data flow of pharmaceutical supply chain information to create transparent drug transaction data. To identify the shortcomings of the existing approaches in the area of the pharmaceutical supply chain, we conducted a systematic literature review (SLR) to deeply understand the problems and the solutions that are being used to overcome such challenges. By applying the SLR approach, 16 relevant studies were identified and systematically reviewed in this thesis. In the current literature, there is no model that uses artificial intelligence techniques to store pharmaceutical supply chain information on-the-fly to make decisions and control entities end-to-end. In this research, we investigate the use of AI methods to address the aforementioned research issues and make decisions intelligently. The intelligence built into PharmaBlock provides automated and reliable mechanisms to perform the following:

- classify the stored data to allocate and give different accessibility levels for data
- alert pharmacies to accelerate the process of selling nearly expired drugs
- determine an optimal selling price for a drug in a decentralized marketplace
- determine future drugs demand to reduce wastage.

The thesis concludes with possible solutions to the identified research questions and the time frames for addressing these issues.

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Chapter 1

Introduction

1.1 Introduction

Delivering medicine to the right person at the right time is one of the highest priorities in the healthcare system. In developing countries, the distribution of drug products is an urgent issue due to the complexity of managing the pharmaceutical supply chain due to system requirements because there are many stakeholders and also, there are time constraints associated with delivering medications to patients to ensure their well being [3]. A pharmaceutical supply chain is a supply chain that consists of a set of players, processes, information, and resources which transfers raw materials and components to finished products or services and delivers them to the customers [4].

Optimizing the process and management of the pharmaceutical supply chain is now a major research challenge. The drug industry is facing particular problems such as finding a balance in terms of producing enough drugs to meet demand, tracking every entity in the supply chain, and reducing the number of counterfeit drugs [5]. The imperfect supply chain system and the lack of traceability are the two main reasons for the appearance of counterfeit drugs. This problem lies in the lack of shared information between nodes in the supply chain system; for instance, manufacturers do not have information about the location of their products after exporting their drugs [6]. Hence, there is an urgent need for better tools to manage information on drugs.

The risk to human life due to counterfeit medicines being sold on the black market without medical permits is a serious issue. The World Health Organization (WHO) [7] reported increased sales of counterfeit drugs around the world, and this is expected to increase by 35% over the next five years. Developing countries in Africa and Asia are the main areas suffering from the sale of counterfeit drugs, with around 30% of total medicine sales being counterfeit. The security and traceability of pharmaceutical companies and pharmacy distributers is becoming increasingly important in an attempt to control this problem [8, 9]. Many technologies have been used to improve drug supply chain systems, but there are still many uncontrolled issues. From this point of view, the introduction of blockchain technology can reap several benefits. Drugs for example can be tagged and scanned to be stored securely in a distributed ledger; this ledger will be updated in real-time as the drugs are transferred from one entity to another in the supply chain [10].

According to a survey conducted by Supply Chain Management (SCM) World, the aggregate revenue for the top 20 pharmaceutical companies around the world is about \$496 billion a year and the cost of throwing away medications which are due to expire is about \$10 billion per annum [11]. SCM World collaborated with the Future of Healthcare Advisory Board to identify the annual amount of wasted medicines which are discarded due to expiry with the goal of reducing this wastage [12, 13]. Discarded medication also has an adverse impact on the environment and the economy. Therefore, it is critical to find alternative strategies to reduce drug wastage [14].

Accordingly, many studies have suggested increasing online pharmaceutical sales, such as e-marketplaces, to solve problems such as making drug selection more transparent with the price depending on user demand. The Food and Drug Administration (FDA), which is an agency in the US Public Health Service that provides a number of health-related services [15], can use its power to force drug manufacturers to make changes to drugs, change safety labeling and marketing practices, or completely remove a particular medication from the market.

Buyers and sellers of physical products can connect through the internet via e-market platforms. Such platforms also provide payment services that facilitate easy remittance of funds for completed transactions [16]. However, one disadvantage of an online marketplace is that an extra charge is imposed on the purchaser when a product changes hands and a third-party payment system is used which is linked to the online marketplace [17]. Also, purchasers' personal data can be hacked or stolen which makes an online marketplace untrusted.

E-Marketplaces can sell nearly expiring over-the-counter drugs for a reduced cost. This results in a saving to the consumers and increased revenue for the manufacturers [18]. Developing decentralized marketplaces has become necessary to enhance and increase the effects of network services on the platforms, improve recommendation systems for goods, and to simplify transactions between peer-to-peer in a trusted manner [19, 20]. A decentralized marketplace is an online eCommerce platform that is executed on the blockchain. This style of marketplace has many advantages in terms of improving the efficiency of marketing. It is true that traditional online marketplaces have limitations such as: security and privacy issues, high maintenance costs, and a lack of transparency. On the other hand, a decentralized marketplace based on blockchain technology offers a secure and trusted environment and using an intelligent decision-making-based ”just-in-time inventory system , it will provide consumers with a highly secure environment. Furthermore, it will also assist in achieving one of the main objectives of this research which is to reduce the wastage of drugs by selling nearly expired medicines to consumers like pharmacies. This system will reduce costs by minimizing warehouse needs. This marketplace will receive any over-the-counter drugs that are about to expire and will display them in the decentralized marketplace to sell them for an optimal price.

Blockchain technology was introduced to solve the problems associated with digital payments and trust. The main role of this technology is to eliminate the traditional third party where buyers and sellers are connected directly [21]. This allows both parties to deal directly and securely with each other without sharing their private information; in other words, blockchain has the ability to make a secure payment mechanism and a mutual agreement between buyers and sellers in the network [22]. Gathering information across the supply chain into one simple single system for all stakeholders to achieve transparency, security, and oversight of the end-to-end users has now become a requirement.

1.2 Statement of the Problem

The previous section outlines some critical issues related to the pharmaceutical supply chain. Currently, data is stored and managed by large manufacturers and pharmacy retails using their own centralized system. Several existing approaches and methods that allow pharmaceutical information to be stored and shared between the healthcare provider and other stakeholders in a centralized manner have been discussed in the literature. These methods are not very useful in terms of data utility. The need for the reliable sharing of pharmaceutical information between various stakeholders is essential, requiring a technology that adds traceability and visibility to supply chains like the pharmaceutical supply chain to provide all the information from end to end. It is also important to have a secure framework for the data flow of pharmaceutical supply chain information to create transparent drug transaction data.

Blockchain technology offers a distributed framework that can positively affect the process of assembling and sharing pharmaceutical information between the relevant stakeholders, such as the FDA [1], manufacturers, distributors, pharmacy retails, and researchers.

1.3 Blockchain Technology

Blockchain is currently one of the most discussed and widely adopted innovations and it has also attracted the attention of researchers in various fields. From financial to manufacturing, education and healthcare. Several applications have emerged in recent years, all emphasizing the significant impact that it is expected to have as the competition for digital economies intensifies, due to its increasing popularity. In 2008, the first blockchain was conceptualized by Nakamoto [23] and has since undergone development and implementation in numerous applications beyond digital currency. Nakamoto published the initial whitepaper on blockchain technology in 2009, outlining the technology's decentralized nature, which rendered it highly effective in improving digital trust. Blockchain has continued to emerge as a technique that will change the way we interact [23].

Blockchain technology allows the concept of a decentralized environment, meaning that every piece of information or transactions cannot be controlled by a single authority. Every completed transaction will be permanently stored in a public ledger. The main purpose of inventing the technology of blockchain is to solve the double records problem without the need of a central server.

Researchers and scientists generally define blockchain technology as a data structure in the form of a permanently recorded transaction chain [10]. Every transaction is cryptographically signed and verified to generate a single block by all miners. Miners are defined as nodes that use software to solve complex mathematical problems and this process results in the block being successfully added to the chain [24]. This chain is made up of linked blocks and each block contains the timestamp of the previous block, a cartographic hash, and some other transaction data details. This creates secure, synchronized, and shared timestamped records that are resistant to modification [25]. Blockchains are typically managed by a peer-to-peer network for use as a publicly distributed ledger, where nodes collectively adhere to a protocol to communicate and validate new blocks.

1.3.1 Blockchain structure

Blockchain technology is currently attracting the attention of many researchers due to the benefits it provides to a vary array of technologies. Researchers have defined blockchain as an open source distributed ledger that is immutable and contains valuable data and information that can be shared over the network [26]. Fundamentally, blockchain is a chain of blocks that produce a public ledger. This ledger holds immutable records of transaction and data. The data are controlled by smart contracts. Smart contracts have been defined as self-executed codes that can be executed by miners over the network to verify specific predefined terms and conditions [27]. Any transaction is registered in a public, secure, and permanent ledger with a timestamp and a number of other details. Researchers define the blockchain paradigm as a digital decentralized public ledger and is a series of recorded valid transactions in chronological order. Blockchain can provide a generalized framework for implementing decentralized computer resources. This requires the blockchain database to be managed autonomously by individuals within a peer-to-peer network protocol, using a distributed timestamping server [28].

Records in blockchain can be authenticated by mass collaboration or consensus algorithms over the network [29]. Each computer resource can be counted as a single state-machine and cryptographically used to securely transition between states. When a new state-machine is created (new computer resource has joined in the network), the nodes encrypt logic that defines valid state transitions and send it to the blockchain [30].

1.3.2 Block Structure

A blockchain is a chain of blocks containing a complete and unalterable record of transactions. Blocks within the blockchain encompass valid transactions and are linked to each other via the cryptographic hash of the preceding block. This process guarantees the accuracy and authenticity of the information stored within each block, starting from the initial block in the chain [31].

A block is designed to have a block header, which contains a previous block hash, and every block has a unique parent block. The block that has no parent block is known as the Genesis block. The block body is usually composed of a list of transactions and a transaction counter. The maximum number of transactions included in the block body is dependent on the block size [32]. When using valuable data in an untrustworthy environment, blockchain uses a digital signature based on symmetric cryptographically. A digital signature works by allowing each user to own a pair of keys, private and public.

Each time a user signs a transaction, the private key will be used for this purpose and will be kept confidential. Then, these digitally signed transactions are broadcast over the network. A digital signature goes through two phases: the signing phase and the verification phase. The signing phase means the broadcast transaction will encrypt the data with the private key and then send them via the network. In the validation phase, a node will validate the value using the public key of the senders [33]. A typical digital signature algorithm used in blockchain is called the Elliptic Curve Digital Signature algorithm [34, 35].

1.4 Blockchain for AI

The centralized nature of AI may lead to the possibility of data tampering. As this data is stored in a centralized system, it is possible that the data may be hacked and easily manipulated and furthermore, data provenance is not guaranteed [36, 37]. This will obviously lead to risky AI outcomes due to the use of a single data store. Hence, the concept of decentralized AI has recently emerged. Blockchain is considered to be a trusted platform and AI algorithms are able to work with huge volumes of data. The idea of using decentralized AI is to increase trust and security when sharing data stored on the blockchain for processing and performing data analytics and decision making without the need for trusted third parties. Smart contracts, which are widely used with blockchain platforms, have the ability to control transactions between nodes, make trusted and accurate decisions that are verified and validated by all mining nodes of the network [38].

1.4.1 Combining Blockchain and AI

AI algorithms rely on data that can learn to make final decision. Data that are cryptographically signed and validated in blockchain servers after all mining nodes are agreed is permanently stored in the distributed ledger. Machine learning algorithms work better when these algorithms take data from a platform that is secure, trusted and reliable. The results of the machine learning algorithms are stored as a new transaction in blockchain and a block will be generated. The outcome of combining AI and blockchain is a secure, decentralized, and trusted decision for valuable and sensitive data. Combining these two technologies results in significant improvements to secure important data in different fields including medical, financial, trade, and governance.

1.5 Pharmaceutical Supply Chain System

One of the highest priorities in any healthcare system is the delivery of medicine as a strategic product. Nowadays, the management of pharmaceutical supply chains has become more complex as it requires the participation of different stakeholders. Pharmaceutical companies play an important role in the drug supply chain in terms of managing the quantity and quality of medicines and their delivery to the right place and the right customers at the agreed time.

A supply chain refers to a collection of individuals, procedures, information, and assets that facilitate the transformation of raw materials and components into completed products or services and subsequently provide them to customers. A pharmaceutical supply chain comprises distinct checkpoints throughout the drug manufacturing and distribution process. As a supply chain may encompass numerous stages and locations, it is intricate, thereby posing difficulties in tracking all events that occur within it.

Sourcing, production, distribution, pharmacy retails, third-party service providers and the final consumers are the stages which are part of the pharmaceutical supply chain. The supply chain also encompasses all logistics operations, manufacturing activities, and functions related to marketing, sales, product design, finance, and information technology. Every checkpoint within the supply chain possesses a centralized database for storing its respective information.[39].

1.6 Challenges Faced by the Current Pharmaceutical Supply Chain System

Researchers have proven the effectiveness of many of the developed models applied to pharmaceutical supply chain systems. The pharmaceutical supply chain is very complex due to different objectives, the regulatory nature of the industry, and the stakeholders and the organizations of pharmaceutical supply chains, making the task of managing the supply chain all the more difficult, which can lead to problems.

There are many issues and challenges facing the current pharmaceutical supply chains as stated in the literature:

1. It is nearly impossible to control a large number of vendors due to the lack of demand information due to the centralization of data [40] .

2. There is no visibility of the inventory and shipments [41].

3. There are many issues which increase drug wastage annually [42].

4. There are many issues related to counterfeit drugs which cause unfavorable patient reactions [43].

5. There are Several manufacturing problems can arise, including the blending of incorrect raw materials, cross-contamination arising from the production of multiple drugs in the same facility, or inadequate labeling of the finished product [44].

6. Transportation and retailer issues including mishandling and improper temperature controls [45].

7. Storage and warehousing issues such as improper temperature controls or improper handling in the warehouse [46].

The currently used technologies in the pharmaceutical supply chain are unable to capture all data in the system. In this thesis, we design a framework that will be able to record all information from end-to-end in an immutable ledger in a trusted manner.

To tackle some of these challenges, this thesis develops an intelligent framework to enhance and improve different parts of the architecture of the pharmaceutical supply chain. Blockchain can be applied to the pharmaceutical supply chain to achieve the following improvements [22, 47]:

- **Provenance Tracking:** This is very important in a field such as pharmaceuticals which contains a huge number of elements in their supply chains. Hence, it has become almost impossible to trace and track every record. This leads to a lack of transparency, additional costs to the pharmaceutical supply chain and also negatively affects customer relations which ultimately leads to a dilution of the drug's brand name. In blockchain-based supply chain management, the historical records of any drug product will be kept forever and can be traced through the blockchain from its origination to the final user or to where it is at any moment. Tracking product information becomes easier with the help of embedded sensors and RFID tags. With blockchain, delay is reduced as drugs are not stuck in the supply chain as it is possible to track drugs in real time with blockchain and the possibility of misplacement is rare [48]. Moreover, provenance tracking can be used to detect fraud in the pharmaceutical supply chain [49].

- **Cost Reduction:** According to a survey of The American Productivity and Quality Center (APQC) and the Digital Supply Chain Institute (DSCI) of supply chain employees [50], more than one-third of people stated that using blockchain technology in a supply chain can have the positive affect of reducing costs. Blockchain technology can help to reduce the overall cost of tracking products through the supply chain in real time while the security of each transaction is still guaranteed.

- **Establishing Trust:** Trust in complex pharmaceutical supply chains with many participants is required for smooth operations. Applying blockchain technology to a pharmaceutical supply chain will increase trust between different nodes along the pharmaceutical supply chain because of the immutable nature of blockchain which is well-designed to prevent tampering and establishing trust [51].

- **Interoperable:** Blockchain allows data to be more interoperable between pharmaceutical supply chain nodes and as a result, it is easier for companies to share information and data with different stakeholders, such as manufacturers, suppliers, and vendors [52].

1.7 Objectives of this Thesis

The overall thesis objective is to develop and evaluate an intelligent pharmaceutical supply chain based on blockchain. This main objective will be achieved by addressing the following five sub-objectives:

- **Objective 1:** Design a framework that can intelligently store pharmaceutical supply chain information in the blockchain.
- **Objective 2:** Develop an intelligent mechanism that generates alerts. This alert system is part of the AI layer in *PharmaBlock* and derives insights based on the underlying data stored in *PharmaBlock*.
- **Objective 3:** Design a decentralized marketplace platform based on blockchain using smart contracts and intelligent decision making centred on a just-in-time alert system to sell drugs at an optimal price to other consumers.
- **Objective 4:** Develop an intelligent predictive analytical and reliable method to compute future drug demand requirements for manufacturers, based on the previous years' consumption, taking into account the yearly population growth and the amount of past wasted drugs which will be recorded in the blockchain.
- **Objective 5:** Validate the developed approaches by implementing them as a software prototype, and evaluate and test the effectiveness of the proposed methods by comparing them with existing systems in terms of accuracy.

1.8 Research Contribution

This proposed research aims to develop and design an intelligent blockchain for storing and classifying data to assist end users such as pharmacies and patients. This can also help researchers, large manufacturers, the FDA, and other stakeholders to assess and manage several activities inside the blockchain. In order to do this, we propose the use of PharmaBlock which intelligently stores pharmaceutical data.

Therefore, our research contributions are as follows:

1. To design an end-to-end framework, *PharmaBlock*, that can help a pharmaceutical supply chain store its information on-the-fly and document and record any transactions in the system using blockchain. Additionally, this system will classify the stored data to allocate different access levels to ensure data privacy.

2. To find effective ways of selling nearly expired drugs before their expiry date and to develop an early warning system to alert pharmacies of nearly expiring drugs and remind them to sell their drugs in the marketplace.

3. To add value to the data stored in the blockchain by creating an opportunity for consumers, by:

    - setting up the marketplace.
    - giving them a platform on which to purchase products.

4. To design an intelligent system which decides when to purchase a product, when to sell a product, and at what price to sell it. Additionally, to build a demand forecasting model to address the current lack of a prediction model, which means that manufacturers have very little idea of future drug demand which results in drug wastage every year.

1.8.1 Scientific Contribution

- This is the first research to propose a mechanism to store public and private information deferentially on the blockchain. To achieve this goal, we use the concept of sub-chaining.

- This is the first research to develop intelligent methods for sharing drug information using smart contracts between different nodes in the pharmaceutical supply chain based on blockchain.

- This is the first research to propose the use of a personalised date-based early warning system (DBEWS) to predict when a drug is soon to expire in blockchain.

1.8.2 Social Contribution

- This research will add value to the data that is stored in the blockchain by creating an opportunity for consumers by setting up a platform for the decentralized market- place to purchase drugs in blockchain using recommendation systems.
- From the pharmaceutical entities' perspective, this is the first study to provide a way by which the stakeholders can access data over a blockchain and use this data in a respective field, such as research or drug quality management
- Intelligent mechanisms will increase and enhance user's trust in using and joining pharmaceutical supply chain.

1.9 Thesis Plan

To achieve the objectives of this study, this thesis is organized in nine chapters. A brief summary of each chapter follows:

Chapter 2: This chapter provides a systematic literature review of the existing literature on the pharmaceutical supply chain system in general and the use of blockchain technology specifically. The main objective of this chapter is to clarify that the issues we address in this thesis have not been previously addressed and resolved in previous research.
Chapter 3: This chapter outline all the issues and concerns that are to be addressed in this thesis. This is done by formulating research questions from these issues. Then, these questions are used in creating research objectives which will be the main aims of the research study.
Chapter 4: This chapter presents the research methodology for this thesis to address

the limitations identified in the literature review. Specifically, the design science research approach has been chosen for this purpose.

Chapter 5: This chapter presents the solution developed to address research objective 1. In precise terms, a *PharmaBlock* platform is built to document and record any transaction that is done in the pharmaceutical supply chain system using blockchain technology. Additionally, a model is developed to classify the stored data to allocate different access levels to ensure data privacy.

Chapter 6: This chapter includes a detailed description of the proposed algorithm and develops a date-based early warning system to generate an alert to inform pharmacies to take action in relation to nearly expired drugs. This is the solution to research objective 2.

Chapter 7: This chapter presents a novel solution to create a decentralized marketplace to obtain the maximum benefit from nearly expired medicines. An intelligent method is proposed to provide optimal prices for the marketplace. The chapter addresses objective 3 of this research.

Chapter 8: This chapter provides an intelligent predictive analytic algorithm to predict the future demand of drugs to reduce the amount of drug wastage. The chapter includes a detailed description of an intelligent approach that uses statistics to predict the future needs for drugs. This chapter addresses objective 4 of this research.

Chapter 9: This chapter concludes the thesis by providing a summary of all achievements of this research and what can be done in the future to expand this research.

1.10 Conclusion

This chapter introduced the pharmaceutical supply chain system, artificial intelligence and blockchain technology. The combination of artificial intelligence and blockchain technology was also discussed as a means to address a range of issues in the pharmaceutical sector. The problem statement of this thesis was highlighted, and all the challenges faced by the current systems of pharmaceutical supply chain were also discussed. The chapter also listed the scientific and social contributions that this research will make.

In the next chapter comprises a systematic review of the relevant literature. The purpose of this review is to ensure that the issue being investigated in this study has not already been resolved in prior research.

Chapter 2

A Systematic Literature Review

2.1 Introduction

The previous chapter defined the problem statement of this thesis and introduced both blockchain and artificial intelligence (AI) technologies and discussed their combination. We also described the working of the current pharmaceutical supply chain system and the related challenges faced by the current systems. The contributions of this thesis, both social and scientific, were presented at the end of the chapter. This chapter presents a systematic literature review (SLR) on pharmaceutical supply chains based on blockchain technology. The main purpose of reviewing all the relevant studies is to ensure that the issues addressed in this thesis have not been solved in the previous literature. Some of the key requirements of a pharmaceutical supply chain are listed.

As with any new technology, there are several open research issues that exist in the wide implementation of the pharmaceutical supply chain. The objective of this chapter is to understand these current issues by conducting an SLR. The SLR focuses on the following four areas in which pharmaceutical supply chain-based blockchain has limitations:

1. classifying the stored data to allocate different access levels to ensure data privacy.

2. alerting pharmacies to accelerate the process of selling nearly expired drugs.

3. determining an optimal selling price for a drug in a decentralized marketplace.

4. determining future drug demand to reduce wastage.

The need to address these limitations is explained in the following section of this thesis. The structure of the rest of this chapter is as follows: section 2.2 presents the key requirements of an intelligent blockchain platform-based pharmaceutical supply chain. In section 2.3, the process adopted to shortlist the papers chosen for the SLR is discussed, including the search criteria and the inclusion and exclusion criteria. Section 2.4 presents a summary of all the shortlisted papers and an analysis of the 16 selected studies. Section 2.5 discusses the research gaps in the existing studies from the requirements perspective. Lastly, section 2.6 concludes the SLR chapter.

The contents of this chapter have been published in the " International Journal of Web and Grid Services"

2.2 Key Requirements From a Blockchain Platform

This section discusses the key requirements of the blockchain platform and compares the existing literature. A blockchain platform is a distributed ledger that has valuable data and information that can be shared securely over the network [26]. Every transaction on the blockchain is registered in a public, secure, and permanent ledger with a timestamp and a number of other details. Researchers have also defined the blockchain paradigm as a digital decentralized public ledger and is a series of valid transactions in a chronological order. Blockchain can provide a generalized framework for implementing decentralized computing resources and can be managed autonomously by individuals within a peer-to-peer network protocol using a distributed timestamping server [28].

In addition to focusing on creating an intelligent environment for the wide application of blockchain, pharmacy retailers and manufacturers have several requirements too, defined as follows:

2.2.1 A secure platform which allows different information access levels (Req:1)

Managing and tracing the stream of information received from many participants over the pharmaceutical supply chain is a complex procedure. Most of the participants in a pharmaceutical supply chain have their own centralized system to document their data and they never share it with other participants due to a lack of trust. This reluctance to share information causes problems related to failure in managing the supply chain system and other problems that may place human lives in danger. Finding an effective and reliable framework from end-to-end to support the mechanisms of sharing data between multiple pharmaceutical supply chain nodes is an urgent issue. In particular, it is necessary to design a framework that can document and record any transaction that is done in the supply chain system and also provides a smart technique to organize different levels of access to this information.

2.2.2 A decentralized network which provides a just-in-time alert system (Req:2)

According to [53], over-the-counter medication retail sales doubled from 2008- 2021 due to the increased number of patients and the increased consumption of medications. The economic and environmental impact of drug wastage is multifaceted. Therefore, the increasing number of nearly expired medicines has become a global issue. From a pharmacy retailer's point of view, a decentralized detection system model is necessary to intelligently and proactively generate alerts in relation to nearly expired drugs. Once these alerts are generated, pharmacy retailers must find ways to sell these nearly expired drugs to whomever needs them.

2.2.3 A decentralized e-marketplace to help sell over-the-counter products for an optimal price (Req:3)

The Internet enables different sectors to interact to create new opportunities between multiple sellers and buyers in a real-time marketplace [54]. An e-marketplace allows companies to interact with each other, eliminate all geographical barriers and expand their business globally to reap more profits in new markets that were once out of reach [54]. These marketplaces also offer payment services that make it easy to pay for transactions. However, the marketplace always asks for additional fee on customers who use a third-party payment system associated with the platform. Furthermore, the risk of a buyer's private information being compromised makes traditional marketplaces unreliable. As a result, there is a need to create a decentralized marketplace that can improve network services and facilitate secure transactions between users.

2.2.4 A smart system which helps manufacturers predict the demand for each drug (Req:4)

Billions of dollars are being wasted due to the imbalance in the production of medicines compared to demand. Generally, large manufacturers use their own centralized system to manage and store data. A lack of shared information between multiple nodes in the pharmaceutical supply chain is the main reason behind the imbalance between supply and demand. Therefore, after exporting their drugs, manufacturers then do not know anything about their products. To address this complex issue, significant research has been performed and data have been collected to minimize this problem. From a manufacturer's point of view, providing a trusted and secure end-to-end environment is necessary so they can share information which will address the problem of drug wastage.

These four requirements are the pillars of our investigation of the existing methods and approaches in the literature to determine whether they provide technical solutions to address these requirements. Therefore, a comparison of questions and their answers will be listed to determine whether the literature addresses these issues. The following section explains the approaches in the existing literature to shortlist papers for the purposes of conducting an SLR.

2.3 Method adopted for shortlisting the valid literature for SLR

The main focus of this SLR is to survey the existing literature to identify the issues and challenges related to pharmaceutical supply chain information in sharing data between various entities in the supply chain using blockchain. Additionally, it aims to provide intelligent solutions for stakeholders and consumers to reduce drug wastage and obtain a benefit when using the drug marketplace. The scope of this SLR is limited to an investigation of the existing literature to identify the problems in the existing literature with adding features to benefit every single entity in the supply chain. Thus, in this section, we adopt an SLR approach [55], which is a step in Design Science Research (DSR), to systematically identify the use of blockchain in pharmaceutical supply chain management, its challenges, and solutions. The SLR is a structured and organized method used to identify, choose, and combine current literature that is related to the research question under consideration [55]. To ensure the quality of the literature review, this study includes citation and evaluation procedures to complement the basic SLR approach.

In this section, we detail the SLR process to identify the relevant literature to be reviewed in our study. Five steps are adopted for this process:

Step 1: Searching the literature → this step is to define the search terms.

Step2: Data source selection and search strategies → identifying the data sources and process of retrieving the literature.

Step 3: Inclusion and exclusion criteria for selection → the selection criteria are defined to help extract the relevant literature.

Step 4: Quality evaluation → Each of the articles or journal papers are reviewed based on two quality evaluation criteria.

Step 5: Data analysis → After reviewing the selected studies, data is extracted and recorded.

2.3.1 Step 1: defining terms for searching the literature

The key terms that need to be defined at this stage are:

1. **Search terms:** To start the SLR process, the related terms must be carefully selected, hence, we only included studies related to pharmaceutical blockchain and its applications. The keywords used to find the relevant studies are as follows: "Cryptocurrency" "Bitcoin", "Distributed Ledger"," Permission-less", "Permissioned", "Pharmaceutical", "Medical Drugs", "Counterfeit Drugs", "Drugs Supply Chain", "eHealth", "Smart Contracts", "Consensus Algorithms".

2. **Publication time of the records:** For this SLR, we included studies written in English and published between 2008 when the concept of blockchain was introduced by Nakamoto [56] and 2023.

3. **Information required from the selected studies:** The information required for every record is the abstract and the full text document. We only included papers that relate to blockchain and its implementation, applications, and challenges in the pharmaceutical sector. Studies were excluded if their focus was not on the area of blockchain, pharmaceuticals, or smart contracts.

2.3.2 Step 2: Data source selection and search strategies

In this study, we used the following notable scientific digital libraries and search engines:

- ACM Digital Library (www.dl.acm.org)

- MDPI Open Source (www.mdpi.com)

- IEEE Xplore (www.ieexplore.ieee.org/Xplore)

- Elsevier ScienceDirect (www.sciencedirect.com)
- SpringerLink (www.link.springer.com)
- ResearchGate (www.researchgate.net)
- Google Scholar (www.scholar.google.com)

The papers selected for this SLR are industry papers, qualitative and quantitative studies, and scientific academic studies. In the first filtration stage, the papers were filtered based on the keywords detailed in section 2.3.1. We selected papers that contain at least two of the keywords listed in section 2.3.1.The results were saved and a database was created. We excluded articles that were written for workshops, posters, reviews, and pre-print articles. In total, we retrieved 98 papers using this research strategy. Some studies were excluded in this step based on their publication date which reduced the number of papers to 78. The remaining studies were subject to further criteria of inclusion and exclusion as described in the following section.

2.3.3 Step 3: Inclusion and exclusion criteria for selection

Only those studies that meet the inclusion criteria are selected for this SLR and the exclusion criteria are used to reject studies.

- **Inclusion criteria:**
  1. Must contain meta-analyses of multiple scientific studies.
  2. Must include a defined search process, research questions and data extraction.
  3. Must be related to the study area.
- **Exclusion criteria:**
  1. Duplicate studies are excluded.
  2. Written in a language other than English.

3. Contain informal literature reviews without defined research questions or no defined search process.

Table 2.1 summarizes the stages of selecting the relevant literature for this SLR process. From the 82 studies retrieved in the first filtration stage, the titles of each study were evaluated to identify studies that contains the search terms. If the article contains the search terms, the paper was selected, otherwise the paper was excluded. By following this procedure, the total number of selected articles was reduced to 35.

Finally, the abstracts of the 31 papers were read carefully to identify the ones to be included in the final stage. The articles with relevant abstracts were included in the next filtration stage, otherwise they were excluded. By undertaking this filtration procedure, the total number of selected articles was reduced to 27. Table 2.1 lists the SLR selection process.

The SLR process was carried out over multiple phases to ensure appropriate coverage. The first SLR was carried out in 2019 and in 2020, the SLR was updated to include recently published articles. Then, in 2021,2022 and 2023, it was updated again to ensure all the related published studies were included.

2.3.4 Step 4: Quality evaluation criteria

The 27 papers selected from the knowledge database were critically evaluated based on the following seven quality evaluation criteria:

- QE1: Are the aims of the research clearly stated?
- QE2: Does the paper cover relevant work and explore the research topics comprehensively?
- QE3: Was the framework appropriately designed to address the aims of the research?

Evaluation Stages	Method	Assessment criteria
First Stage	Search for keywords from online digital library	Using the identified search terms
Second Stage	Included only papers depending on their titles	If title relevant → Accepted; Else→ Rejected
Third Stage	Included only papers depending on their keywords	If paper keywords relevant → Accepted; Else→ Rejected
Fourth Stage	Included only papers depending on their abstracts	If abstracts relevant → Accepted; Else→ Rejected
Fifth Stage	Obtain selected papers and critically apprise studies	Discusses Data relevant→ Accepted; Else → Rejected

Table 2.1 Scientific Assessment Process.

- QE4: Was the data analysis sufficiently accurate?
- QE5: Is the evidence for the findings stated clearly?
- QE6: Does the paper provide future directions?

Any paper which has at least two ‘yes’ answers to the evaluation criteria questions is included in this SLR. Of the 27 papers, only 23 satisfied the criteria.

2.3.5 Step 5: Data analysis and shortlisted literature

The 23 papers were carefully studied and the quality of each was ensured by following the quality criteria proposed by [57]. Only the most relevant papers were selected after studying them in detail. After applying the quality criteria proposed in [57] to the 23 articles, we excluded 3 papers at this stage, leaving 20 articles for the final data analysis and synthesis based on its scope, topic area, summary of its research questions and answers.

The final 20 selected studies were carefully evaluated against the quality criteria. Based on the analysis, the selected papers were categorized into one of the broad areas of "technology in a pharmaceutical supply chain" and "blockchain-based pharmaceutical supply chain" as describe in Table 2.2. The selection of these fields was based on their direct relevance to the source of the requirements (Req 1 to Req 4) to facilitate a blockchain-based pharmaceutical supply chain arise. A summary of the papers related to each field ,limitations and challenges is presented in the following section.

Study Number	**Year of Publication**	**Title of Study**	**Category**
Study 1 [58]	2017	Trace and track: Enhanced pharma supply chain infrastructure to prevent fraud	Blockchain
Study 2 [22]	2017	Blockchains everywhere a use-case of blockchains in the pharma supply-chain	Blockchain
Study 3 [59]	2018	Blockchain technology in pharmaceutical industry to prevent counterfeit drugs	Blockchain
Study 4 [60]	2018	Pharmaceutical cold chain management: Platform based on a distributed ledger	Blockchain

Study 5 [61]	2018	Governance on the drug supply chain via gcoin blockchain	Blockchain
Study 6 [62]	2020	Drug Governance: IoT-based blockchain implementation in the pharmaceutical supply chain	Blockchain based IoT
Study 7 [63]	2021	Blockchain-enabled pharmaceutical cold chain: Applications, key challenges, and future trends	Blockchain
Study 8 [64]	2021	Blockchain Medledger: Hyperledger fabric-enabled drug traceability system for counterfeit drugs in the pharmaceutical industry	Blockchain
Study 9 [65]	2020	A Blockchain and Machine Learning-Based Drug Supply Chain Management and a Recommendation System for Smart Pharmaceutical Industry	Blockchain based machine learning
Study 10 [66]	2021	A Blockchain-Based Approach for Drug Traceability in the Healthcare Supply Chain	Blockchain

Study 11 [67]	2021	Traceability and Detection of Counterfeit Medicines in the Pharmaceutical Supply Chain Using Blockchain-Based Architectures	Blockchain
Study 12 [68]	2021	A Proposed Architecture for Pharmaceutical Supply Chain-Based Semantic Blockchain	Blockchain based IoT
Study 13 [69]	2021	A Blockchain-Based Approach to Detect Counterfeit Drugs in the Medical Supply Chain	Blockchain
Study 14 [70]	2021	Securing E-health Networks from Counterfeit Medicine Penetration Using Blockchain	Blockchain
Study 15 [71]	2021	Enhanced Drug Anti-Counterfeiting and Verification System for the Pharmaceutical Drug Supply Chain using Blockchain	Blockchain
Study 16 [72]	2022	A robust drug recall supply chain management system using the Hyperledger blockchain ecosystem	Blockchain

Study 17 [73]	2022	Blockchain implementation in pharmaceutical supply chains: A review and conceptual framework	Blockchain
Study 18 [74]	2022	Smart contract diffusion in the pharmaceutical blockchain: the battle of counterfeit drugs	Blockchain
Study 19 [75]	2022	Secure and transparent pharmaceutical supply chain using permissioned blockchain network	Blockchain
Study 20 [76]	2023	lockchain-based solution for Pharma Supply Chain Industry	Blockchain

Table 2.2 Studies that meet the quality evaluation criteria

2.4 Analysis of selected papers against the requirements

To thoroughly analyze the studies selected for the SLR, we divided them into the three following groups:

- **Cold pharmaceutical supply chain:** Pharmaceutical cold chain refers to the logistics and planning to ensure a drug is kept at its recommended temperature from the point of manufacturing to the point of final customer.

- **Non-Cold pharmaceutical supply chain:** The pharmaceutical supply chain refers to a network of participants, procedures, data, and assets that facilitate the transfer of raw materials and components into final products or services, and ultimately deliver them to consumers.

- **Governance of the pharmaceutical supply chain:** This describes corporate governance within the context of a pharmaceutical company, where policies and regulations are employed to guide business choices, ensure legal compliance, and fulfill commitments to stakeholders.

2.4.1 Cold pharmaceutical supply chain

Some pharmaceuticals require strict environmental conditions throughout the transit process to ensure they are transported safely and to avoid deterioration. The management of pharmaceutical products that can be adversely affected by temperature and humidity fluctuations, light, and vibrations is known as pharmaceutical cold chain logistics [77]. Cold pharmaceutical supply chains are defined as a temperature-controlled supply chain system from end-to end [78]. These types of pharmaceutical supply chains have strict requirements to ensure the quality of the products being shipped and their integrity must be maintained from the point of production through all phases of transportation, to where the products reach the end user. Cold supply chains would benefit from a technology like blockchain. For example, data can be updated in real time and the products can be tracked as they move from one stage to another. This enables supervisors to take action in case, for example, a temperature excursion occurs. Solutions based on blockchain technology have the capability to automatically monitor environmental factors across the entire supply chain, document this information, and generate timely notifications if any errors are detected. This frees up technicians from having to conduct routine monitoring tasks.

In [60], the authors represented the architecture of a platform for cold drug supply chain management and solutions and explained the framework of a cold pharmaceutical supply chain using a Hyperledger distributed ledger. This work explains how the transaction stores and tracks the delivered products and the associated environment data. The authors of this work used the Sawtooth framework developed by Intel to collaborate and to track products using a scalable infrastructure. Participation in the cold supply chain network requires each participant to join the network with one validator node.

The work in [63] addressed how blockchain technology meets the requirements of a pharmaceutical cold supply chain, such as a pharmaceutical digital identity, serialization and traceability, data integrity, transparency, and waste management. The authors demonstrated that the main benefit of using blockchain in a pharmaceutical cold supply chain is to enable data integration, secure transactions, serialization, and traceability. The study also examined the primary advantages and disadvantages of the cold supply chain in the pharmaceutical industry and provided examples of projects that incorporated blockchain technology.

Table 2.3 lists the existing studies on cold pharmaceutical supply chains that use blockchain technology and evaluates the literature against the four requirements identified earlier in this chapter (Req1-Req4).

Study	Description of the Study	Issues and Limitations	Requirements of pharmaceutical			
			Req1	Req2	Req3	Req4
			X = Not met the requirements			
Study [60]	Presents an architecture to track products in a pharmaceutical cold supply chain using Hyper- ledger and the Saw- tooth framework.	The study does not provide any mechanism to push data to the permissioned blockchain.	✓	X	X	X
Study [63]	Describes how blockchain technology can meet the requirements of a pharmaceutical cold supply chain and discussed drawbacks of a pharmaceutical cold supply chain using case studies.	The study does not provide solutions to the listed challenges.	X	X	X	X

Table 2.3 Existing studies on pharmaceutical cold supply chain and their description, issues and limitations

2.4.2 Non-cold pharmaceutical supply chain

One of the top priorities in any healthcare system is to deliver medicine. Many healthcare systems experience several difficulties in achieving their goals as they do not properly address how medicines are managed, supplied, and used. The pharmaceutical supply chain has become complex due to the number of stakeholders that participate in the supply chain. The shortage of medication and the misuse of pharmaceuticals not only result in monetary damages but also have a considerable effect on patients. As a result, managing each step of the process, from acquiring, storing, to distributing pharmaceutical products, is crucial for pharmaceutical companies both in terms of finances and organizational aspects.

Pharmaceutical supply chain issues have been addressed by several authors from different points of view. Additionally, many studies have addressed the use of different technologies to optimize the work in the supply chain. Recently, several studies have applied blockchain technology to pharmaceutical supply chains to obtain a benefit. The rest of this section briefly describes the most important work in this field.

The work in [59] explains the use of permissioned blockchain technology to add traceability and visibility which means to provide all the information over drug distribution to drug manufacturers and drug regulatory authorities, and also to add security to the pharmaceutical supply chain from manufacturers to consumers. Moreover, this study shows the positive effects on the patients after they used the drugs which was recorded on a database for future statistics.

In paper [58], the author proposed a novel blockchain technology combined with the IoT framework called Global Data Plane (GDP), which can help in communication and the management of data between different nodes. This proposed system builds a high trace and track level of a scalable and trusted system for the pharmaceutical industry by modelling a large infrastructure IoT-scale system. In this work, the authors implemented this system using Tendermint which is divided into two components: blockchain consensus engine, and generic application interface.

In [22] the authors presented a framework called modum.io AG using a combination of IoT and blockchain technology to access data immutability, while reducing the costs in the pharmaceutical supply chain. The main goal of this work is to give detailed insights into how modum.io AG uses blockchain technology in the area of pharmaceutical supply chains using smart contracts to assess the temperature automatically. However, this work presents how to check the temperature through the supply chain without tracking any other important factors in the pharmaceutical supply chain.

The author of [64] proposed a novel track and trace pharmaceutical system called Medledger based on a Hyperledger Fabric blockchain platform to solve the problem of transferring and tracking drugs. The main goal of the proposed system is to allow the stockholders to securely execute and record transactions over the pharmaceutical supply chain to enhance integrity and reliability and also to provide maximum transparency and traceability in the system. This decentralized framework allows only participants who authenticate themselves using digital certificates to access it.

The work in [65] presented and implemented a framework of blockchain and machine learning -based pharmaceutical supply chain management and a recommendation system. The authors of this study suggested a framework consisting of two primary components: a drug supply chain management system based on blockchain technology and a machine learning-based system for recommending pharmaceuticals to consumers. The initial module's purpose is to supervise and record the process of delivering drugs in the intelligent pharmaceutical industry. In the second component, the authors utilized N-gram and LightGBM algorithms to suggest the highest-rated medications to customers. In this work, the authors stated that the proposed system can help pharmaceutical companies eliminate the problem of counterfeit drugs.

The work in [66] investigated the challenges of tracking drugs within the supply chain. The authors proposed a blockchain-based solution to enhance tracking and tracing drugs in a decentralized manner. The authors used the Ethereum blockchain platform to provide automated access to the recorded transactions made by participants.

The proposed system architecture allows the stockholders to interact with the smart contract to access data on-chain. This work was tested and validated and it also discussed the cost and security analysis of the proposed solution.

The authors of [67] proposed a solution for pharmaceutical supply chain traceability using blockchain technology. The authors used Ethereum and Hyperledger Fabric platforms and compared the performance of the two approaches under the use case of the pharmaceutical supply chain. After comparing the two different approaches, the authors found that the Hyperledger-based approach is more efficient in terms of scalability, security, and it is more enterprise friendly. Unlike Ethereum, accountability in the public blockchain in Hyperledger is easier to achieve as the authors stated in this work.

The architecture in [68] introduced a framework that enhances security in the pharmaceutical supply chain, improves transit and storage, and improves patient satisfaction and trust. The author of this work combined the Internet of Things, the Semantic Web, and blockchain to increase the transparency and visibility of the pharmaceutical supply chain. The proposed architecture of the pharmaceutical supply chain-based semantic blockchain comprises three layers. The first layer is the IoT to represent hardware and wireless sensor networks as well as RFID, the second layer is the Semantic Web which represents the knowledge, relationships, transactions of IoT and the blockchain, and the third layer is the semantic metadata to annotate all the objects and data types.

The work in [69] introduced a new system to detect counterfeit drugs in the pharmaceutical supply chain by adopting a Hyperledger Fabric platform. This peer-to-peer framework-based smart contract makes the process of delivering drugs to patients more secure and much faster. The authors of this work divided the proposed framework into four parts: the ingredient verification process to ensure the authentication of each element, the drug sample verification process to ensure the authentication of each drug, the QR code and drug delivery verification process, and the observation and revoke process. These four steps of the proposed solution verify the medicine before and after production.

The proposed framework solution in [70] describes the process of delivering drugs in the drug supply chain with a high level of transparency. The proposed work is based on recording the logistic requirements of drugs on the blockchain platform from the starting point of the supply chain manufacturing to the patient. Hence, if any counterfeit drugs are introduced to the supply chain, they will be rejected by the proposed system. The decentralized framework has eleven computational nodes and is based on the Hyperledger Fabric platform and the proposed system was tested and compared with three other systems, namely the Conventional system, the Vledder et al. system, and the Mouaky et al. system.

The authors of [71] proposed a verification system that is able to enhance the tractability of drugs in the supply chain. They used two germane smart contracts namely: shiDrug and receiveDrug to ensure the system safely moves drugs over the pharmaceutical supply chain using Hyperledger Fabric. Only valid actors in the supply chain can execute smart contracts, while the final customers were able to verify the drugs using a unique identifier. The authors of this work implemented the proposed system in three parts: blockchain development, API development, and user interface development. The proposed system was evaluated based on transaction throughput, latency, and resource consumption.

The work in [72] presents a framework that allows manufacturers to monitor drugs in the supply chain to improve transparency. The work also minimizes both cost and time with a focus on transferring drugs forward and backward in the supply chain. The forward chain works in a similar way to any traditional pharmaceutical supply chain, while the backward supply chain focuses on managing the supply chain in case of a drug recall. The contributions of this work are increasing the transparency for the pharmaceutical supply chain and reducing both cost and time. The authors of this work used the Hyperledger blockchain to implement their proposed work.

Assurance of drug safety and integrity is a challenge faced by the pharmaceutical industry as states in [73]. The authors mentioned that counterfeit drugs are prevalent because of the level of supply chains transparent. The study explains how blockchain technology can help by providing a secure and transparent platform for tracking and verifying the movement of drugs in the supply chain. In addition, this paper shows how blockchains are being implemented in pharmaceutical supply chains and discusses use cases, including drug traceability, counterfeit prevention, and supply chain efficiency. The authors highlight the potential benefits of blockchain implementation in the pharmaceutical industry, including improved patient safety, reduced costs, and increased trust between stakeholders.

The authors of the work [74] propose a conceptual framework using the smart contracts in the pharmaceutical industry to reduce the problem of counterfeit drugs. The work shows an overview of pharmaceutical industry based blockchain and also the authors discuss in details how smart contracts can enhance the effectiveness of pharmaceutical industries based blockchain technology by increasing the level of transparency and automating certain processes. Then, the authors of this work examine the current state of smart contract adoption in the pharmaceutical industry, and highlight the benefits of using smart contracts, such as increased transparency, reduced costs, and improved data integrity.

The authors of this work [75] aim to create a safe and secured pharmaceutical supply chain platform by using a permissioned blockchain network as a result of many challenges that faced the pharmaceutical industries. The authors state that permissioned blockchain platform can help in tracking and control drugs throughout the supply chain and it could also increase the privacy. The paper presents a conceptual framework for the implementation of a permissioned blockchain network in the pharmaceutical industry. The framework includes the establishment of governance and standards, network architecture design, and smart contract development for tracking and verification. The authors believe that a permissioned blockchain network could significantly improve the safety and efficiency of the pharmaceutical supply chain, as well as address the issue of counterfeit drugs.

This work [76] discusses the challenges that the pharmaceutical industries are faced, which can be the lack of transparency, security in supply chains, and the appearance of counterfeiting medication. This study provides an overview of pharmaceutical supply chain based blockchain technology such as drug traceability, authentication, and supply chain optimization. The authors also discuss the challenges of implementing a blockchain-based solution in the pharmaceutical industry, including regulatory compliance, technical complexity, and collaboration between stakeholders.

Table 2.4 lists the existing studies on non-cold pharmaceutical supply chains that use blockchain technology and evaluates the literature against the four requirements identified earlier in this chapter (Req1-Req4).

Study	Description of the Study	Issues and Limitations	Requirements of pharmaceutical			
			Req1	Req2	Req3	Req4
			X = Not met the requirements			
Study [59]	This study addresses the benefit of using blockchain in pharmaceutical supply chains by adding traceability and value when the patients review the medicines after using them for future statistics.	The mechanism was not implemented on actual cryptocurrency.	X	X	X	X
Study [58]	This study proposes a combined framework using IoT and blockchain technologies to manage and track data flow between different nodes and also modelled a large infrastructure IoT scale system to increase trust.	The designed framework has privacy issues because the proposed model uses a public blockchain which means untrusted nodes can access the network.	X	X	X	X

Study [22]	This study presents the modum.io framework using both IoT and blockchain technologies to use some sensor devices to track temperatures and the humidity of the pharmaceutical sup- ply chain to ensure quality control over the transported product.	This work needs to add more factors to be tracked to ensure the quality of the products	X	X	X	X
Study [64]	This study develops a framework called MedLedger which is a peer-to-peer tracing system to track drugs using the collaboration between chain-codes.	The implemented system faced issues related to scalability, privacy, standards and regulations	X	X	X	X

Study [65]	This work implements a system using blockchain and machine learning for medicine in the supply chain and it is provided by a recommended system.	The proposed work not implemented or tested in real time pharmaceutical companies to measure the performance of the system, and the accuracy level of the recommendation system needs to be improved	X	X	X	X
Study [66]	This study develops an off- chain decentralized storage for more efficient traceability.	Transparency of the proposed system was not fully achieved from end to end.	X	X	X	X
Study [67]	This study describes two different approaches to using blockchain, one using Ethereum and the other using Hyperledger Fabric and then compares the performance of these two approaches.	Some IoT device tracking issues are not covered or discussed.	X	X	X	X

Study [68]	This study proposes an architecture using semantic web technology to enhance the capability of IoT-based blockchain.	The proposed work is not fully implemented or evaluated.	X	X	X	X
Study [69]	A A blockchain-based approach is proposed for integrating pharmaceutical laboratories in the supply chain.	The work does not provide any solution to the security issues listed.	X	X	X	X
Study [70]	This study develops a system to allow patients to check the authenticity of the drugs over the supply chain.	The solution was not implement in real-world scalability.	X	X	X	X
Study [71]	This work develops a system to enhance drug anti-counterfeiting using the Hyperledger blockchain platform.	The work in this paper does not provide solution to the security issues listed	X	X	X	X

Study [72]	This work develops a system that allows manufacturers to track all drugs from point to point using Hyper- ledger blockchain.	The designed system is limited to be local business and can not be a cross-trade business.	X	X	X	X
Study [73]	This study presents a framework using blockchain technology to track drugs of the pharmaceutical supply chain to ensure quality control over the transported product.	This work needs to add more factors to be tracked to ensure the quality of the products.	X	X	X	X
Study [74]	This study proposes an architecture using blockchain technology to enhance the capability of pharmaceutical supply chain based blockchain.	The proposed work is not fully implemented or evaluated.	X	X	X	X

Study [75]	This study propose a framework to track drugs in pharmaceutical supply chain using permissioned blockchain to increase the security.	Some important issues and factors are not covered or discussed.	X	X	X	X
Study [76]	implemented a framework to reduce counterfeit drugs using blockchain. This provides the tools to improve tracking drug along the supply chain.	implementation only focused on storing drug data in the blockchain, without mentioning any mechanism	X	X	X	X

Table 2.4 Existing studies on pharmaceutical non-cold supply chain and their description, issues and limitations

2.4.3 Governance of a Pharmaceutical Supply Chain

The purpose of pharmaceutical supply chain governance is to increase efficiency and benefit every participant by sharing information on logistics to improve cooperation between the government and other participants. Open government is defined as "a culture of governance based on innovative and sustainable public policies and practices inspired by the principles of transparency, accountability, and participation that fosters democracy and inclusive growth" [79]. Open information is essential to achieve transparency. This means all the drug supply chain transaction data are protected by the government blockchain system which is open to all participants.

The authors in [61] suggested the use of a Gcoin blockchain framework, a governance model of the drug supply chain, to improve transparency, the efficiency of information exchange, and to protect data in the drug supply chain with an open government organization. The main aim of this work is to transform centralized governance to a decentralized system incorporating every participant in the network to improve the efficiency of information exchange in combination with an open government and decentralized autonomous organization (DAO) regulation model to ensure a secure and transparent drug supply ecosystem.

The work in [62] merged IoT technology with blockchain and implemented it in the pharmaceutical supply chain to reduce the amount of counterfeit drugs. The authors of this work investigated novel pharmaceutical governance based on IoT and blockchain technology, which is a type of distributed ledger technology (DLT) that maintains an immutable record of all transaction information. The authors state that implementing an IoT-based blockchain system provides the tools for the pharmaceutical industry to improve drug governance along the supply chain and as a result, makes healthcare more efficient and reliable.

Table 2.5 lists the existing studies on the governance of pharmaceutical supply chains that use blockchain technology. Further, in this table, we systematically evaluate the literature against the four requirements identified earlier in this chapter (Req1-Req4).

Study	Description of the Study	Issues and Limitations	Requirements of pharmaceutical			
			Req1	Req2	Req3	Req4
			X = Not met the requirements			
Study [61]	Suggested the use of Gcoin blockchain to shift from regulation by government audits to surveillance net (by each participant involved in the supply chain).	Solution provided was not implemented in real world scalability.	X	X	X	X
Study [62]	Implemented a framework to reduce counterfeit drugs using IoT and blockchain. This provides the tools to improve drug governance along the supply chain.	implementation only focused on storing drug data in the blockchain, without mentioning any mechanism for joining the network which is not effective or efficient for a secure platform.	X	X	X	X

Table 2.5 Existing studies on the governance of pharmaceutical supply chains and their description, issues and limitations

2.5 Research gaps in the existing studies from the requirement perspective of a pharmaceutical supply chain

As presented in the previous Table 2.3 - 2.5 researchers have focused on storing data in a pharmaceutical supply chain using blockchain. However, several drawbacks were identified:

1. **The lack of a secure platform to allow different levels of information access**
   Some papers, such as [59], [60], [80], and [63] used a permissioned blockchain platform to increase security and to allow only permissioned nodes to participate in the network. A permissioned blockchain is used because it is more secure than a public blockchain, as only authorized nodes will be granted privileges to push data to the blockchain. A high level of security in an important sector like healthcare is required, but some factors also need to be taken into consideration. Without such an approach, the existing literature does not allow different levels of access for participants in the blockchain platform. None of the existing literature uses any artificial intelligence techniques to classify stored data to use them in a private manner.

2. **The lack of a decentralized network to provide a just-in-time alert system**
   While most of the included studies focused on transferring a centralized pharmaceutical supply chain systems to a decentralized one, intelligent methods need to be included in any pharmaceutical platform. Intelligent engines and alert systems are needed in an important field like pharmaceuticals. None of the existing literature takes into account how pharmacy retailers can obtain a

benefit from nearly expired drugs by alarms being generated to alert them to sell nearly expired drugs using blockchain technology. None of the existing literature develops a personalised warning system to detect expiry dates and push drugs to the blockchain platform.

3. **The lack of a decentralized E-marketplace to help sell over-the-counter products for an optimal price**
   An e-marketplace in any field helps connect buyers and suppliers, adds value, and saves money if it is based on controlled regulations. The studies included in this SLR do not consider the benefit that can be obtained by selling over-the-counter medications that are about to expire for a reduced price. This will not only save the consumer money, it will also benefit consumers who require medication. Furthermore, instead of throwing away nearly expired drugs, which increases environmental pollution and has a negative impact on the economy, they can be sold on the e-marketplace. Hence, consumers can obtain a benefit from nearly expired drugs and they can purchase nearly expired drugs using blockchain technology. None of the existing literature uses any artificial intelligence techniques to automatically predict an optimal selling price for nearly expired drugs.

4. **The lack of a smart system to help manufacturers predict the future demand for each drug**
   Smart systems add value to any field and sector. Some of the studies in this SLR, such as [22], [80], and [62] used other technologies like IoT and RFID in addition to blockchain, which improves the entire system. Adding AI techniques to a pharmaceutical supply chain will support the system from the production stage to the final stage which is drug delivery to patients. To the best of our knowledge, there is no work in the existing literature that adopts AI techniques to predict the demand for each drug.

2.6 Conclusion

This SLR suggests four key requirements that should part of a pharmaceutical supply chain. Such requirements include modelling a secure intelligent information collection and classification and also modelling a smart framework that is able to generate personalized alerts for pharmacy retailers. Other requirements include developing a decentralized marketplace and designing an intelligent approach to predict the optimal price to sell over-the-counter drugs that are nearly expired , and the last requirement is modelling an intelligent approach that helps manufacturers predict the future demand for drugs.

Chapter 3 details the gaps identified based on the SLR reported in this chapter. Also, Chapter 3 provides definitions for the key terms used in this study and presents the research questions and objectives.

Chapter 3

Research Questions and Objectives

3.1 Introduction

This chapter represents the research questions for this research study based on the SLR provided in Chapter 2. These questions help in formulating the our research aims and objectives which are provided in this chapter.

3.2 Gaps in the Literature

The literature review identified the following significant challenges in using blockchain to enhance the service in the drug supply chain:

1. None of the existing literature uses any artificial intelligence techniques to classify stored data to ensure privacy.
2. None of the existing literature has set a personalised early warning system to detect and push them to the marketplace. None of the existing studies take into account how pharmacies can benefit by establishing a decentralized marketplace for selling and purchasing nearly expired drugs using blockchain technology.
3. None of the existing literature is is taking into account how consumers can get the benefit from the nearly expired drugs by setting a decentralized marketplace

for selling and purchasing nearly expired drugs using blockchain technology and predict an optimal selling price for drugs.

4. None of the existing literature use any Artificial Intelligence techniques to automatically predict the future demand of drugs based on the historical data.

3.3 Key Definitions

This section presents the definitions of terms that will be used in this thesis.

Blockchain: Blocks within the blockchain technology contain valid transactions. Each block is made up of the cryptographic hash of the previous block within the chain, providing the link between two blocks. This process ensures that there is integrity within the records stored by each of the blocks [81].

Pharmaceutical supply chain: A pharmaceutical supply chain refers to a network of participants, procedures, data, and assets that facilitate the transfer of raw materials and components into final products or services, and ultimately deliver them to consumers [4].

SKU: A stock keeping units (SKU) is a unique numerical code that a retail establishment assigns to a product for the purpose of distinguishing its price, variants, and manufacturer, as well as for tracking inventory levels within the store [82].

FDA: Food and Drug Administration (FDA) is a department of the Public Health Service that offers a variety of healthcare-related services [15].

Online marketplace: The concept of an online marketplace refers to utilizing electronic communication and digital information processing technology in commercial transactions, with the aim of generating, altering, and redefining relationships between organizations, individuals, or both, for the purpose of value creation [83].

Smart Contracts: Smart contracts refer to a series of computer codes that are carried out by nodes and miners via the blockchain network. They are automated transaction protocols that implement the provisions of a contract. Smart contracts are created to meet typical contractual requirements, such as payment terms, in order to minimize the occurrence of both fraudulent and occasional exceptions, and to reduce the reliance on trustworthy intermediaries [84].

Ardor: Ardor is a blockchain platform that is capable of hosting multiple chains, featuring a unique structure of a parent chain and multiple child chains. The parent Ardor chain provides security for the entire network, while the individual child chains possess various rich functionalities, making them interoperable with one another [85].

3.4 Main Research Question

From the SLR documented in Chapter 2, and the shortcomings outlined in Section 2.5, it is clear that there are several gaps in the existing literature on blockchain-based pharmaceutical supply chains. To address these gaps, the following research question is identified:

How can pharmaceutical information be stored in a reliable manner so that it can be used for privacy-aware intelligent decision making by various stakeholders?

This main research question can be subdivided into the following five sub-questions:

- **Research Question 1:** How can we develop a reliable, smart and scalable framework for collecting and storing data from the pharmaceutical supply chain systems on-the-fly?

- **Research Question 2:** How can we develop an intelligent framework that generates personalised alerts for pharmacy retailers in relation to nearly expiring medicines?

- **Research Question 3:** How can intelligent approaches be used to predict the optimal selling point for drugs which are about to expire?

- **Research Question 4:** How can we develop a data-driven intelligent method to predict the future demand for a drug in the marketplace?

- **Research Question 5:** How can we validate and verify the proposed methods using a proof of concept simulation framework/s?

3.5 Research Objectives

The overall thesis objective is to develop and evaluate an intelligent pharmaceutical supply chain based on blockchain. This main objective will be achieved by addressing the following five sub-objectives:

- **Objective 1:** Design a framework that can intelligently store pharmaceutical supply chain information in the blockchain.
  This objective will be achieved by developing the *PharmaBlock* platform that is built to provide a single system for pharmaceutical supply chains from end-to-end.

Ardor blockchain is chosen to develop this *PharmaBlock* platform as it provides the ability to define a parent - child chain.

- **Objective 2:** Develop an intelligent mechanism that generates personalized alerts in *PharmaBlock* platform.
  This alert system is part of the AI layer in PharmaBlock and derives insights based on the underlying data stored in the *PharmaBlock*. This alert system is part of the Artificial Intelligence (AI) layer in *PharmaBlock* and derives insights based on the underlying data stored in the *PharmaBlock*. An algorithm to derive the date-based alerts based on the personalized value stored on the system will be developed.

- **Objective 3:** Design a decentralized marketplace platform based on blockchain using smart contracts and intelligent decision making centred on a just-in-time alert system to prompt pharmacy retails to sell nearly expired drugs at an optimal price to other consumers.
  The marketplace has an intelligent decision making providing recommendations on the optimal price to sell drugs. A price predictive module will be used to calculate the optimal price for the drugs.

- **Objective 4:** Develop an intelligent predictive analytical and reliable method to compute future drug demand for manufacturers, based on the previous year's consumption, taking into account the yearly population growth and the percentage of past wasted drugs which will be recorded in the blockchain.
  A model will be developed to predict and compute the number of drugs required to meet future demand using machine learning predictive models to help manufacturers produce the required number of drugs. This number will be driven based on the number of previous wasted drugs in a certain area taking into account the population growth. Based on the drug demand in the previous period, we predict future drug demand.

- **Objective 5:**Validate the developed approaches by implementing them as a software prototype, and to evaluate and test the effectiveness of the proposed methods by comparing them with existing systems in terms of accuracy.
  The working of the proposed blockchain-based pharmaceutical supply chain will be evaluated using the Ardor network. This will be done by evaluating its effectiveness to address the four research questions using certain benchmarks.

3.6 Conclusion

This chapter includes the research questions for this study which will be answered in this thesis. It also includes the research objectives that will be achieved using a systematic research approach. In addition, the chapter provides definitions for the key terms used in this research.

In the next chapter, the research methodology and an overview of the solutions for each objective are presented. This research methodology will explain how these objectives can be achieved.

Chapter 4

Research Methodology and Solution Overview

4.1 Introduction

This chapter presents the methodological approach that will be used to address the limitations identified in the literature review in Chapter 2. This chapter provides an overview of the proposed solution and explains how the research questions will be solved. This chapter is organized as follows: Section 4.2 defines the various terms used in the solution of this research. Section 4.3 outlines the selected research methodology and justifies its solutions. Section 4.4 presents an overview of research question 1 to research question 5. Section 4.5 concludes the chapter.

4.2 Keys Definitions

PharmaBlock: In this thesis, we use the term *PharmaBlock* to refer to the platform that provides services to the pharmaceutical supply chain from end-to-end to achieve the prime objective of this research.

4.3 Selected Research Methodology

In this section, to address the gaps identified in this thesis, the design science model is used to achieve the research objectives and goals. An overview of the steps in the design science methodology is presented in Figure 4.1 below [2]:

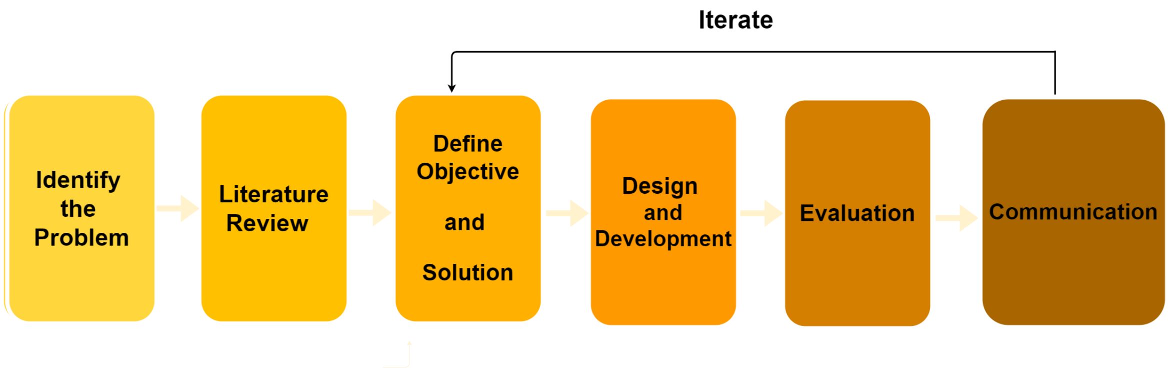


Fig. 4.1 Design science research methodology [2].

The design science research methodology offers a systematic approach to research by developing an initial prototype that is tested to determine if it satisfies the objectives originally identified. This research approach forms the basis for this study, our proposed solution is divided into the six following phases:

- **Phase 1: Identify problem phase:** In this step, we identify the gaps in the existing research on which we want to focus. We identify the problem as the lack of approaches to model a framework for storing pharmaceutical supply chain data on-the-fly.
- **Phase 2: Literature review phase:** In this step, we identified and outlined the gaps in the existing literature by carrying out a systematic literature review (SLR). This process is documented in chapter two of this thesis.

- **Phase 3: Define the research objective and a solution phase:** Based on the outcome of phases 1 and 2, we clearly identify our research objectives. The focus of this research is to design a blockchain approach based on artificial intelligence to store pharmaceutical supply chain data, using prediction methods to systematically and intelligently classify and predict to solve issues in the pharmaceutical field. This phase is detailed in chapters three and four of this thesis.

- **Phase 4: Design and development phase:** In this phase, we develop the artificial intelligence models and blockchain as a proof of concept corresponding to the solutions to research questions 2, 3, and 4. The developed models are part of the overall proposed methodology for storing information on-the-fly. This phase is documented in chapters five to chapter eight of this thesis.

- **Phase 5: Evaluation phase:** In this phase, we evaluate the performance of the developed AI models using a number of well known metrics. This will be done to answer research question five and is described in chapter eight. .

- **Phase 6: Communication phase:** In this phase, the outcomes from the previous two phases will be disseminated by scholarly publications in international peer-reviewed journals and conferences.

The design, development, and evaluation phases are performed iteratively throughout the research project based on the outcomes achieved. This iterative process flows from the partial completion of the research back to the objective definition phase to facilitate a deductive cognitive approach. In other words, as the solution is created and assessed, the iterative process allows for refinement and improvement.

4.4 Solution Overview

This section provides an overview of the PharmaBlock platform that is designed to intelligently store information for the pharmaceutical supply chain.

4.4.1 Overview of solution for RQ1: Architecture of the PharmaBlock

The medical description data that is stored in the PharmaBlock system must be classified for easy access whenever needed. The data classification approach is detailed as follows and is illustrated in Figure 4.2:

- **Stage 1: Information Gathering (Medical Description)** All data are collected by the Intelligent Rule Engine from the pharmaceutical supply chain layer. The medical description information must be entered in a standardized format to be accepted and uploaded as a pending transaction in the blockchain layer, namely Drug ID, Drug Expiry, Drug Name. This information will enable the system to intelligently store the data on the relative chain later as shown in Figure 4.2 below. Different drug companies may have different drug IDs or names for the same medical component. This may lead to drug ID duplication. To avoid this problem, our system will provide a list of drug IDs from which to choose and if a particular drug is not on the list, the drug company can request a new drug ID be added to the list which will be checked via the consensus mechanism for approval.

- **Stage 2: Classification and Labelling Information (Medical Description):** At this stage, the Intelligent Rule Engine labels the information in the medical description and then refactors it into three groups as mentioned to be stored in the relevant chains.

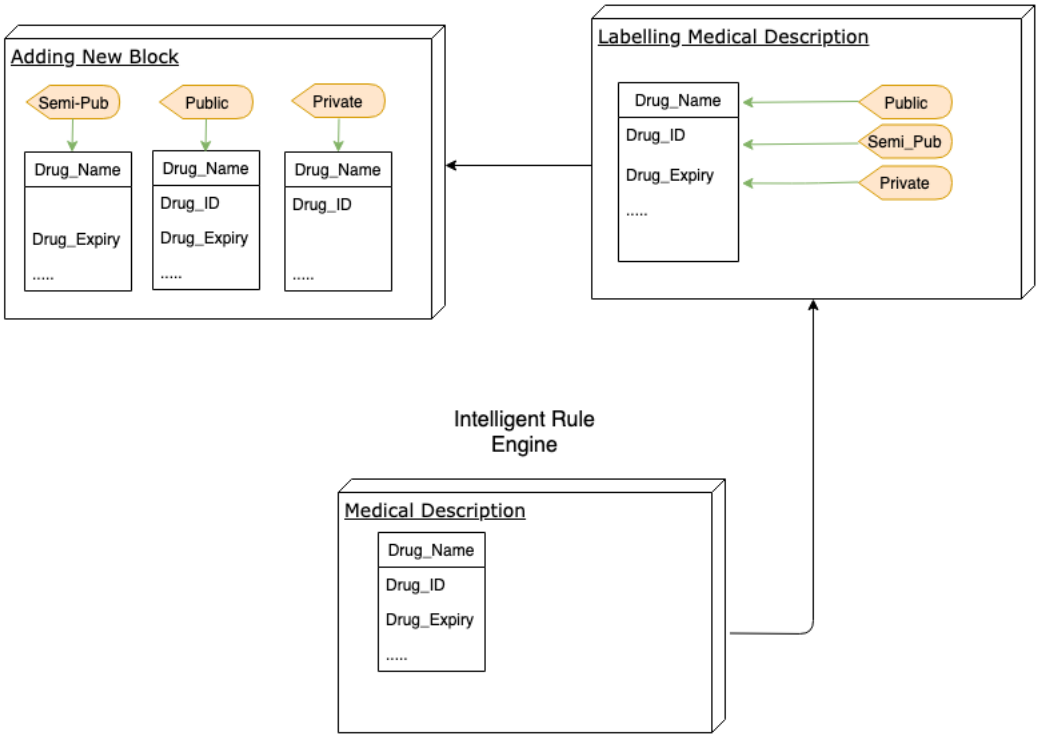


Fig. 4.2 Data Classification Framework within PharmaBlock.

4.4.2 Overview of solution for RQ2: Design An Early Warning Detection Module

Based on the personalized variable value, we present a model in our system called the Early Warning Detection Module (EWDM), which takes this variable value and compares it against the drug batch expiry date; if it is within that, an alert will be automatically generated to the end user.

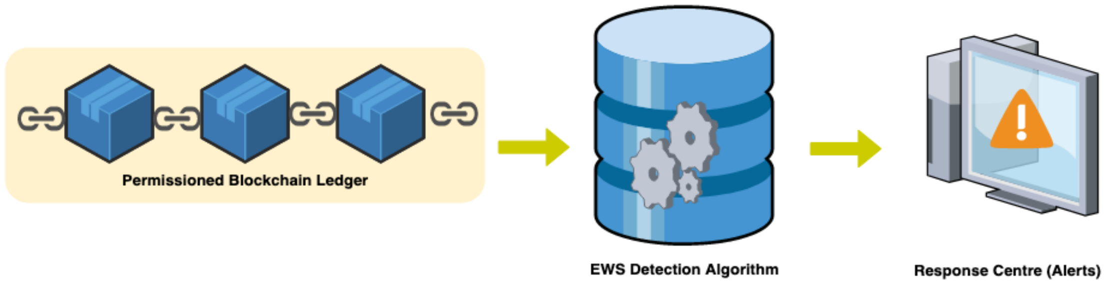


Fig. 4.3 Early Warning Detection Module within PharmaBlock.

The proposed EWDM comprises three components, as shown in the Figure 4.3.

- **Stage 1:** Customer activates the EWS algorithm and provides a personalized value.
- **Stage 2:** PharmaBlock uses the EWS algorithm to find drugs using the personalized value.
- **Stage 3:** EWS generates an alert and provides it to the client.

Once the EWDM has been implemented, pharmacy retailers can place the nearly expired drugs on the marketplace where other pharmacies, hospitals and customers can purchase them at an optimal price..

working of the algorithm is outlined as follows:
Early Warning Detection Module (EWDM) Algorithm *(Window V, Repeat R, Alert Type A)*

4.4.3 Overview of solution for RQ3: Design A Decentralized Marketplace

Figure 4.4 illustrates the steps in developing an optimal price prediction model for the nearly expired drugs.

Algorithm 4.1: Early Warning date-based Algorithm

```
Begin
Store V in the Blockchain
Repeat for every batch in the Blockchain
Compare V with Current date
if V > current date value then
    EWDM ( V, R, A)
else
    Generate an alert A
else
    Send a recommendation
Stop
```

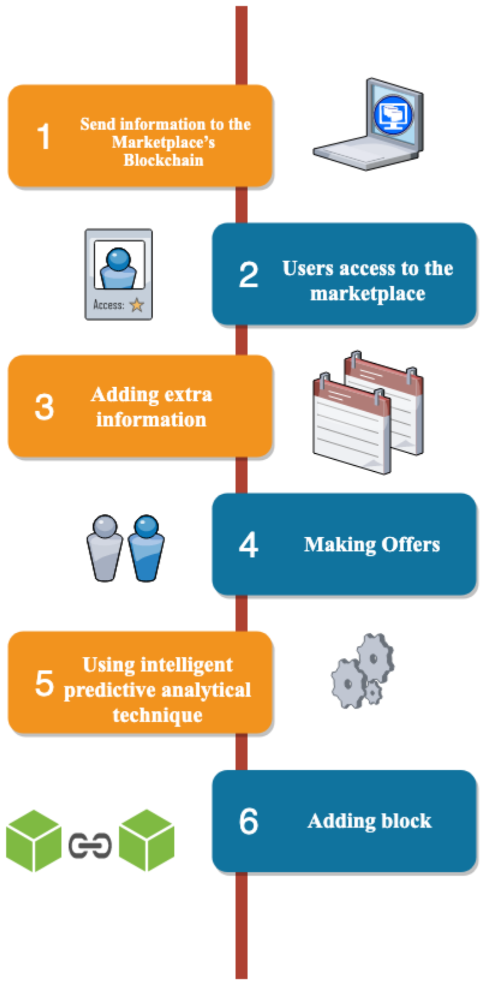


Fig. 4.4 The process workflow of selling drugs in the marketplace

- **Stage 1:** In this step, when a pharmacy retailer wishes to dispose of nearly expired drugs, the public description of the information corresponding to the drugs is encapsulated and stored as a new block. The marketplace is provided with access to the new block. Once this has occurred, the information in the new block is made available on the marketplace.

- **Stage 2:** Users access to the marketplace:Consumers must register to access the marketplace and the information available in the marketplace. Once a user has registered, then they are able to view the information in the marketplace.

- **Stage 3:** Adding extra information: The seller can add extra information to the newly created block start that is needed for the selling process such as: seller information, seller location, number of available batches, selling and base selling price.

- **Stage 4:** Making Offers Multiple consumers visit the marketplace and view the listing and can make offers.

- **Stage 5:** Using intelligent predictive analytical technique: The Price Prediction Module (PPM) uses the aforementioned multiple factors as input to the regression models to determine the optimal selling price.

- **Stage 6:** Adding block: The seller decides to which buyer the product will be sold. Once the payment for the sale is made, the details of the seller and the buyer are added in the block in the blockchain. Once the payment is made, the pending block is added and confirmed on the blockchain as a permanent transaction.

4.4.4 Overview of solution for RQ4: Predict Future Demand

To answer this research question, a model is developed to predict and compute the seasonal number of drugs required to meet future demand using machine learning. To find the solution, we divide this task into the following four stages, as illustrated in Figure 4.5:

- **Stage 1:** Identify the candidate predictive analytical methods to incorporate seasonality. In this research, we identify the following methods:

  1. Multiple linear regression (MLR)
  2. Support vector regression (SVR)
  3. Random forest regression (RFR)

  These three approaches will be used to predict the future drug demand based on historical data.

- **Stage 2:** To analyse the performance efficiencies of the machine learning models in stage one, we use various open datasets.

- **Stage 3 and 4:** We use a programming language to apply various models on the dataset to obtain the best performing model by evaluating the prediction accuracy score for model performance to find the best fit model from the selected ones. The best fit model is chosen for deployment.

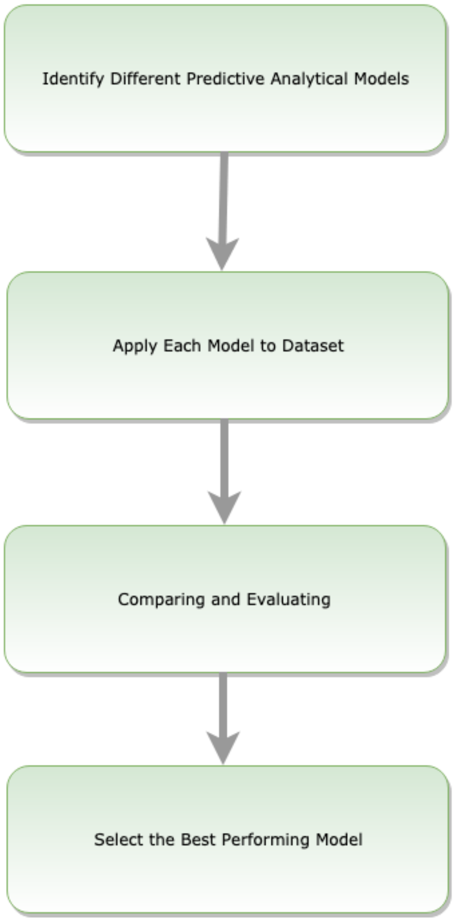


Fig. 4.5 Solution Overview of Predicting the Future Demand of Drugs

4.4.5 Overview of solution for RQ5: Evaluating and validating the Propose Framework

To answer research question 5, the proof of concept developed for the PharmaBlock is verified against the objectives detailed in the previous sections. This process is carried out by comparing our proposed system with the existing systems. The designed proof of concept is validated and tested after satisfying all the requirements. The proposed PharmaBlock platform is evaluated using the Ardor blockchain. This is done by experimenting the effectiveness for addressing Research Question 1 to Research Question 4 along certain benchmarks.

To evaluate our proposed framework PharmaBlock:

– The pharmaceutical information should be stored, classified and shared in such a way that it is easily available for use. PharmaBlock provides information factorization, a feature which is added onto the system throughput and can be validated by comparing the current system information capturing with our system, PharmaBlock. We also evaluate the classification model in the intelligent rule engine using accuracy as a metric.

– To evaluate and compare the method proposed in the solution overview for RQ 2, namely to design an early warning detection system and based on the literature, our proposed system can be validated using the same evaluation metrics that are used in the literature, namely accuracy and response time.

– To evaluate the intelligent methods for selling drugs at an optimal price as a solution for RQ3 and to predict the number of drugs required to meet future demand as a solution for RQ4.

4.5 Conclusion

In this chapter, we discussed the methodological approach used to address the limitations identified in the literature review in Chapter 2. The design science research approach has been selected to be used as a model. Also, the process involved in building PharmaBlock platform was discussed. PharmaBlock will store, classify and share data in such a way that it is easily available for use. Furthermore, an overview of the solution for each of the objectives in this research was presented in this chapter.

The next chapter discusses the pharmaceutical supply chain-based blockchain framework and determination of the current pharmaceutical supply chain.

Chapter 5

An Intelligent Platform for Pharmaceutical Supply Chain Framework

5.1 Introduction

The previous chapter defined the methodological approach that is used to address the gaps identified in the literature review. The overview of the proposed solution and how the research questions are solved are presented in this chapter. The structure of this chapter is as follows: section 5.2 presents the intelligent platform for the pharmaceutical supply chain framework named PharmaBlock as a platform service and its related components are discussed. In section 5.3, we present our secure and intelligent model for data classification as the first key requirement. In section 5.4, an intelligent early warning system model is presented as the second requirement. In section 5.5, we present our intelligent optimal selling point-based marketplace model as our third requirement. Section 5.6 presents our intelligent predictive approach for future drug demand as the fourth requirement. The last section concludes this chapter.

5.2 Intelligent Platform for Pharmaceutical Supply Chain Framework

This section presents the proposed framework PharmaBlock as the base of the data flow of pharmaceutical supply chain information to create transparent drug transaction data. The PharmaBlock framework is divided into five entities as illustrated in Figure 5.1 to address the limitations identified in the literature. We propose the use of blockchain technology for storing all the information emanating from the pharmaceutical supply chain. Each drug manufacturing company has its own bespoke supply chain starting from sourcing the chemicals, compounding them, their subsequent production and the eventual distribution channels. At this stage of the supply chain, data is captured by the pharmaceutical companies using sensors etc. and is stored in the local repositories of the pharmaceutical companies. However, in the current literature, there is no single platform for assimilating this data in a reliable manner. Such a platform can potentially be used to derive insights for various stakeholders in the drug manufacturing industry.

Blockchain technology can be used to serve both the aforementioned purposes, namely the storage of pharmaceutical data in a reliable manner and providing a platform for deriving data insights. To address this issue, in this thesis, we propose PharmaBlock as the base of the data flow of the pharmaceutical supply chain information to create transparent drug transaction data. The architectural PharmaBlock framework is divided into five entities as illustrated in Figure 5.1.

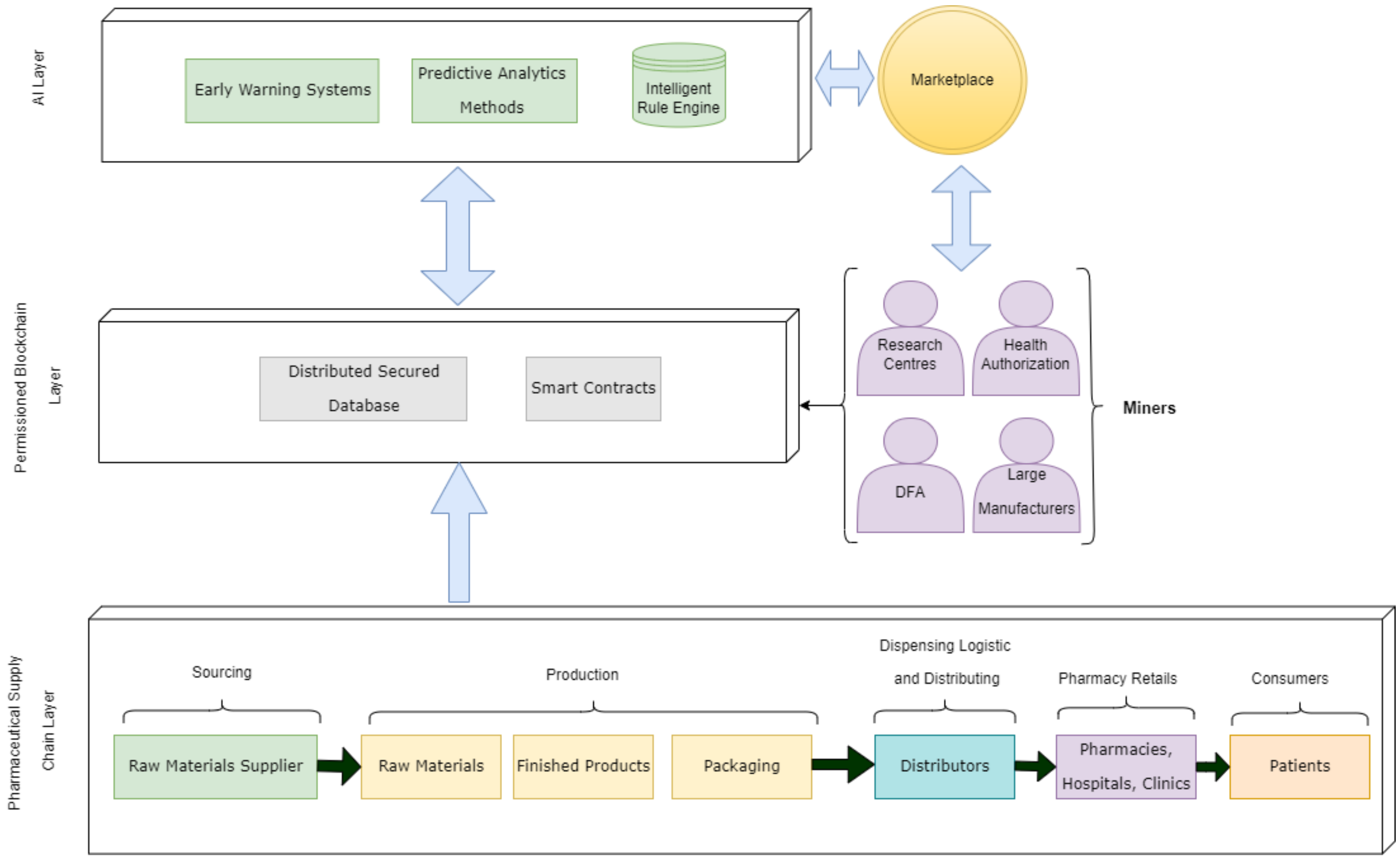


Fig. 5.1 Architecture of PharmaBlock.

PharmaBlock captures and stores the data originating from the entire pharmaceutical supply chain. PharmaBlock is a consortium blockchain. As such, any drug manufacturer can register and enrol to be part of PharmaBlock. However, their membership needs to be approved by the miners of PharmaBlock by majority consensus. Once a pharmaceutical company is part of PharmaBlock, it will be provided with APIs to feed the data streams to PharmaBlock. PharmaBlock has five entities as shown in Figure 5.1 and detailed as follows:

1. ***First Entity: Pharmaceutical Supply Chain layer*** A pharmaceutical supply chain has five stages: sourcing, production, distribution, pharmacy retails, and final consumers, all of which are part of the pharmaceutical supply chain. This is a generic representation and any pharmaceutical company which wants to join the permissioned blockchain layer can do so if they have permission to join. Sourcing in the pharmaceutical field is to create raw materials for drugs, and then place them into drums. All these materials need to be recorded via PharmaBlock. Each drum has a unique number to be tracked over the PharmaBlock network until it reaches the second distention which is production. At this stage of drug production, the drug manufacturers, who are one of the key stakeholders in the pharmaceutical supply chain, pass their information to the Intelligent Rule Engine which records the incoming data stream in PharmaBlock. Pharmaceutical distributors purchase medical products directly from pharmaceutical manufacturers to store them in warehouses and distribution centers across the country. Pharmacy retailers are responsible for dispensing and controlling medicine.
   The information that is captured is the name of the drug, the manufacturing location, date and time stamp, the SKU which is a number assigned to a product by a retail store to identify the price, product options and manufacturer and is used to track inventory in the store [82].
   In this way, only the details of certified and well-known manufacturers or medical companies will be stored in the Blockchain. PharmaBlock is a consortium blockchain. As such, any drug manufacturer can register and enrol to be part

of PharmaBlock. However, their membership needs to be approved by the consortium by majority consensus. Once a pharmaceutical company is part of PharmaBlock, it will be provided with APIs or the mechanism to provide data.

2. ***Second Entity: Permissioned Blockchain Layer*** A key layer in PharmaBlock is the permissioned layer. Within the permissioned layer, our system collects the incoming information streams (referred to as medical description) from the pharmaceutical companies and passes it to the Intelligent Rule Engine for further processing and classification.
   The permissioned blockchain layer contains a smart contract which is an entity that interacts with the permissioned blockchain layer and other entities of PharmaBlock; it plays a very important role by checking the accessibility of other nodes and miners in the permissioned blockchain layer. Additionally, a smart contract finalizes payment in the marketplace, and stores values for the selling point prices of the drugs as well as working associatively with the Intelligent Rule Engine. Please also note that the information is permissioned i.e., the AI algorithms and/or other stakeholders will have access only to the information tagged as public in the blockchain.

3. ***Third Entity: Miners*** Our proposed conceptual framework is designed to include four miners at this stage; if in reality, the work requires additional miner/s, they can join the network as required. For the process of joining the PharmaBlock and to ensure all miners and nodes are trusted, we follow the process of Identity and Access Management. Authorized miners who have already joined the PharmaBlock network can give permission for a new miner to join by majority consensus of the existing miners and using identity and access management processes. The newly joined miner will be labelled as a trusted node. Miners are eligible to access information stored in PharmaBlock using a smart contract depending on their need for this information and their level of access.

The Health Authority, an organization that is responsible for providing strategies for improving pharma health services, identifying pharma needs, and monitoring the development of the health services in general, is one of the miners. Other miners such as the FDA, Research Centres, and large manufacturers can help in improving the pharmaceutical field, increase efficiency and advancement as well as to observe the workflow of producing and manufacturing medicines.

4. ***Fourth Entity: Distributed Marketplace*** The marketplace is a mechanism where people can sell just-in-time drugs which are nearly expired. The marketplace platform is designed for permissioned users only as we want to deal with authorized information only and hence only authorised users who are part of PharmaBlock can provide a listing; however, it is open to anyone to make a purchase using a smart contract. Briefly, the marketplace is for pharmacy retailers to dispose of their nearly expired drugs at an optimal price whenever they wish to sell. The marketplace interacts with the PharmaBlock by extracting some basic information required to dispose of the drugs, such as: how many batches are available to sell? and what is the selling price?

5. ***Fifth Entity: AI Layer*** The AI layer has predictive analytical methods on top of the permissioned blockchain layer; it also has the Early Warning System and Intelligent Rule Engine repository, as shown in Figure 5.2. A brief description of each entity in the AI layer is as follows:

   – **The Intelligent Rule Engine:** The Intelligent Rule Engine's main role in the AI layer is to receive the standard description information (the medical description) from the blockchain layer for all drugs. This medical description comprises the name of the drug, the drug ID, the batch ID, the quantity produced, and the expiry date, etc. Also, the Intelligent Rule Engine works intelligently and associatively with the smart contract to intelligently carry out the classification of the incoming information stream. Then, the entered information is intelligently classified depending on the attributes of the information and preferences of the pharmaceutical companies. The Intelligent Rule Engine intelligently classifies the attributes of the in- coming data streams received from the pharmaceutical supply chain layer as public, private, and semi-public data which is subsequently stored in the blockchain. The process of adding this information in a new block is described in detail later.

- **Early Warning System:** The role of the EWS (within the AI layer) is to intelligent and proactively generate alarms and personalised alerts to pharmacy retailers using PharmaBlock. The alerts correspond to expiring drugs. Furthermore, as a part of the generated alert, the EWS provides the pharmacy retailers with the option to sell the nearly expired drugs. The EWS is part of the AI layer within PharmaBlock that interacts with the permissioned blockchain chain.

- **Predictive Analytical Methods:** These are intelligent methods to predict an optimal selling point to sell drugs, as well as to predict the future demand for the drugs based on the population statistics.

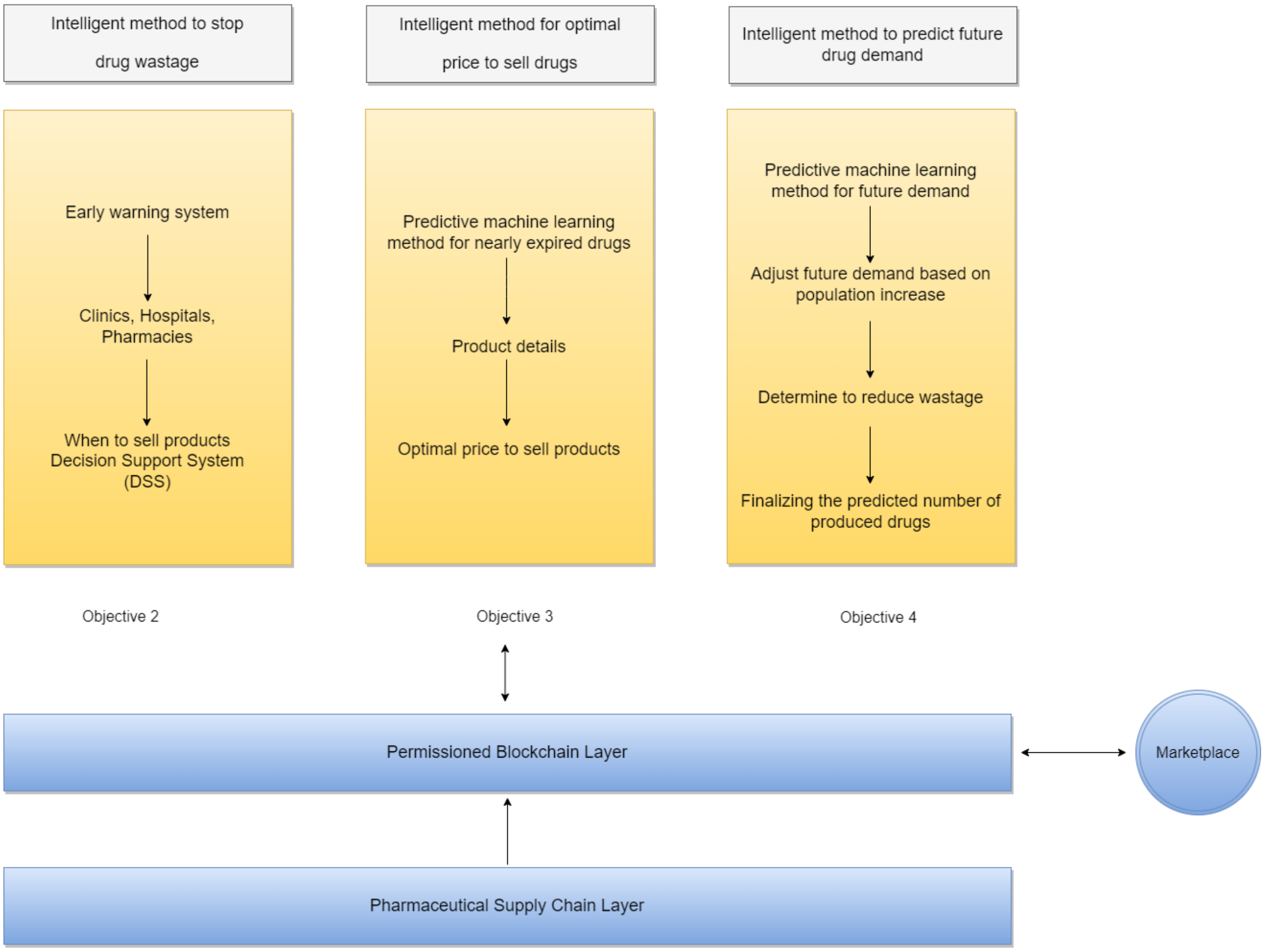


Fig. 5.2 Architecture of AI Layer.

5.3 Modelling a secure intelligent information collection and classification system (Req: 1)

1. 1. The incoming streams from the pharmaceutical supply chain layer are intelligently classified and labelled by the Intelligent Rule Engine and smart contracts into three different categories at the entry stage to allow different levels of access:

   - Public Data
   - Semi-Public Data
   - Private Data

2. Permissioned users (miners and nodes) in PharmaBlock can access different types of permissioned data depending on their access privileges.

3. 3. Drug owners can specify the level of access to the drug information using the smart contracts by following the sub-chaining of block architecture, as shown in Figure 5.3. Smart contracts organize the owner accessibility process to the private and semi-public blocks for eligible nodes.

4. 4. The public classified data is stored in the public block, and the private and semi-public data is stored using the two sub-chains, as described in Figure 5.3.

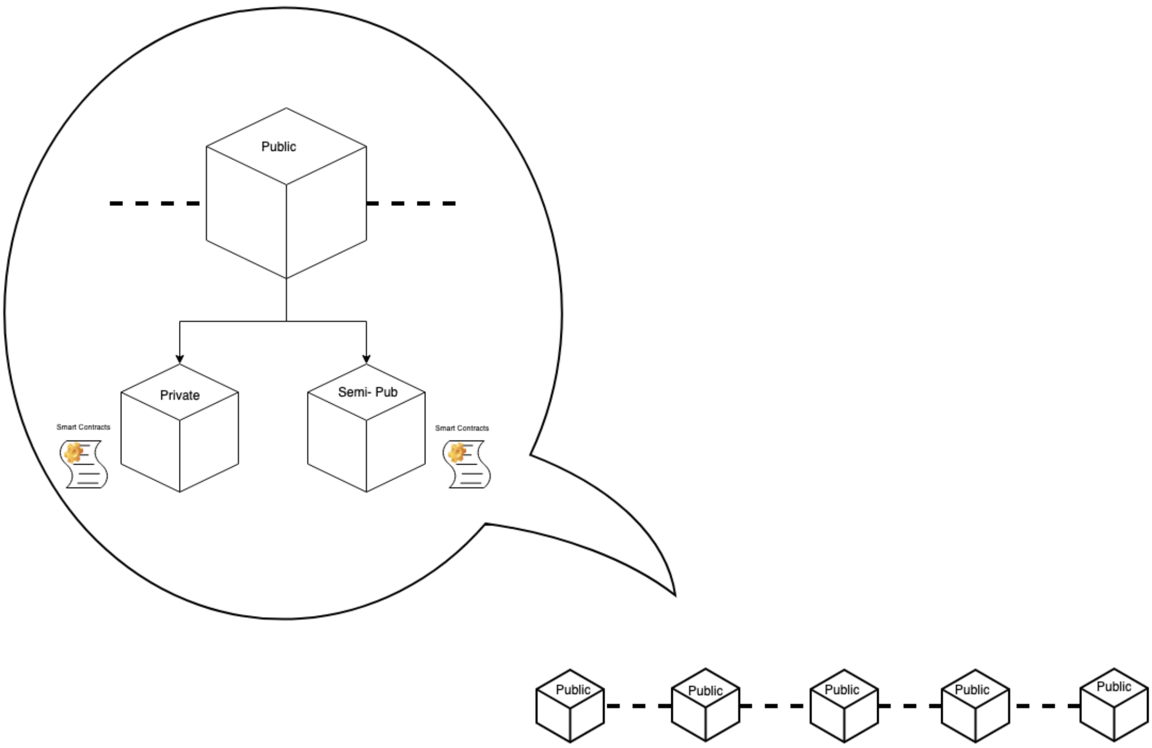


Fig. 5.3 Architecture of Sub-Chaining.

All data in the Medical Description that is stored in our system PharmaBlock must be classified for easy accessing whenever it is needed. The following approach for classification data can be achieved as described below in Figure 5.4:

1. *Stage One: Information Gathering (Medical Description)* All data will be collected and gathered by the Intelligent Rule Engine from the pharmaceutical supply chain layer. Medical Description must have standard information to be accepted and uploaded as a pending transaction in the blockchain layer, such as: Drug ID, Drug Expiry, Drug Name. This standard piece of information will support our system to intelligently store the data to the relative chain later on as shown in Figure 5.4 below. Different drugs companies may have different drug ID or names for the same medical component. This may lead to drug ID duplication. To avoid the problem of drug IDs' duplication, our system will provide a list of drug IDs' to choose from and if not in the list then drug company can request to add a new drug ID to the list, and this new drug ID will be checked via consensus mechanism for approval.

2. *Stage Two: Classification and Labelling Information (Medical Description):* At this stage, the Intelligent Rule Engine will label the information in the Medical Description received and then refactor them into three groups as mentioned before to be stored in the relevant chains.

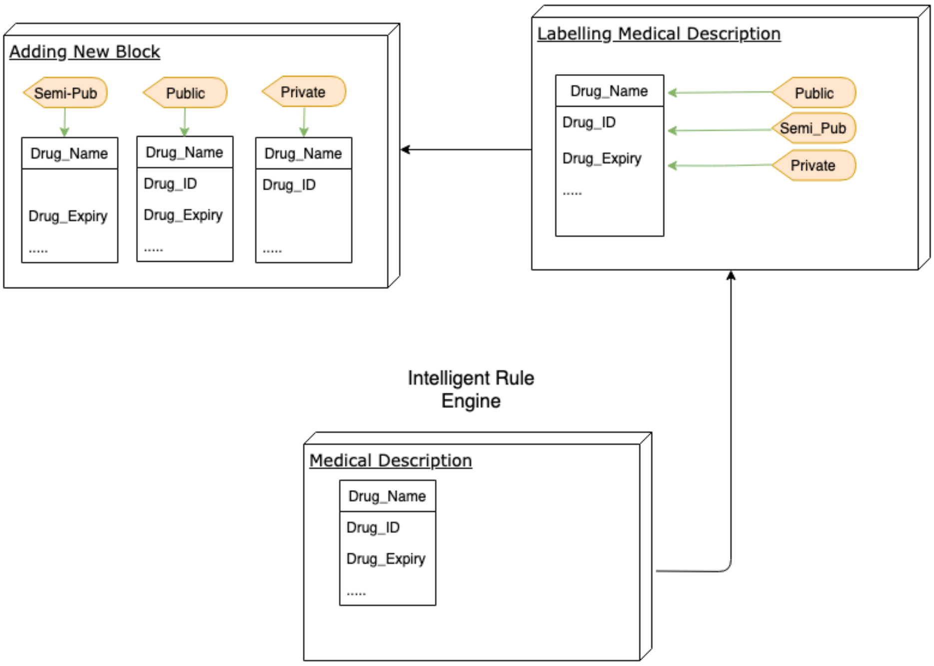


Fig. 5.4 Data Classification.

5.4 Modelling an intelligent framework that generates personalized alerts for pharmacy retailers (Req:2)

To present the end-users with intelligent and bespoke time-based alarms alerting them to drug expiry, we use a warning system. The Early Warning System (EWS) provides alerts and also makes recommendations before the case starts [86]. The date-based early warning system (DBEWS reminds pharmacy retailers of currently stored drugs that are nearly expired, based on the proactive solution and to act proactively against drug wastage. Alerts are sent to the concerned nodes to take action and to obtain a benefit from these drugs by selling them in the marketplace.

The working of the EWS to generate predictive alerts for end users about the impending expiry of drugs is as follows:

the automatic detection of all drugs that are stored in the blockchain using information such as drug expiry date, number of batches and their location, and automated alerts sent to the pharmacy retailers when nearly expiring drugs are detected.
This is achieved by extracting drug information from the permissioned blockchain layer, then an analysis of the drug information is sent via an alert to pharmacies if these drugs will expire in a certain period of time depending on the **personalized value** entered by pharmacy retails. This alert also will suggest that the drugs are sold for an optimal price in a decentralized marketplace, as described in more detail later.
At this stage, we set up a timeline that can be used as a personalized variable value for generating alerts to a pharmacy, **where every end-user sets their preferred time window**. This personalized variable value will generate alerts which will vary depending on the pharmacy and will let the pharmacy retailers know in enough time when drugs will expire to ensure the drugs are released at the right time.

5.5 Modelling an intelligent approach to predict the optimal selling point based marketplace for drugs that about to expired (Req: 3)

5.5.1 Marketplace Brief Description

To achieve (Req :3), a decentralized marketplace needs to be built. A decentralized marketplace is an online eCommerce platform that is executed on the blockchain. This marketplace is for pharmacy retail outlets who want to sell multiple batches of medical drugs prior to their expiry. While only registered users are allowed to sell pharmaceutical drugs on the marketplace, registered and non-registered users (including general consumers and patients) are allowed to use and access this marketplace as long as they have already joined this permissioned blockchain network.

This marketplace targets pharmacy retailers who want to buy/sell a multiple batch of medical drugs before expiry; also, general consumers and patients are allowed to use and access this marketplace as long as they already have joined this permissioned blockchain network. The workflow of the marketplace is illustrated in Figure 5.5 .

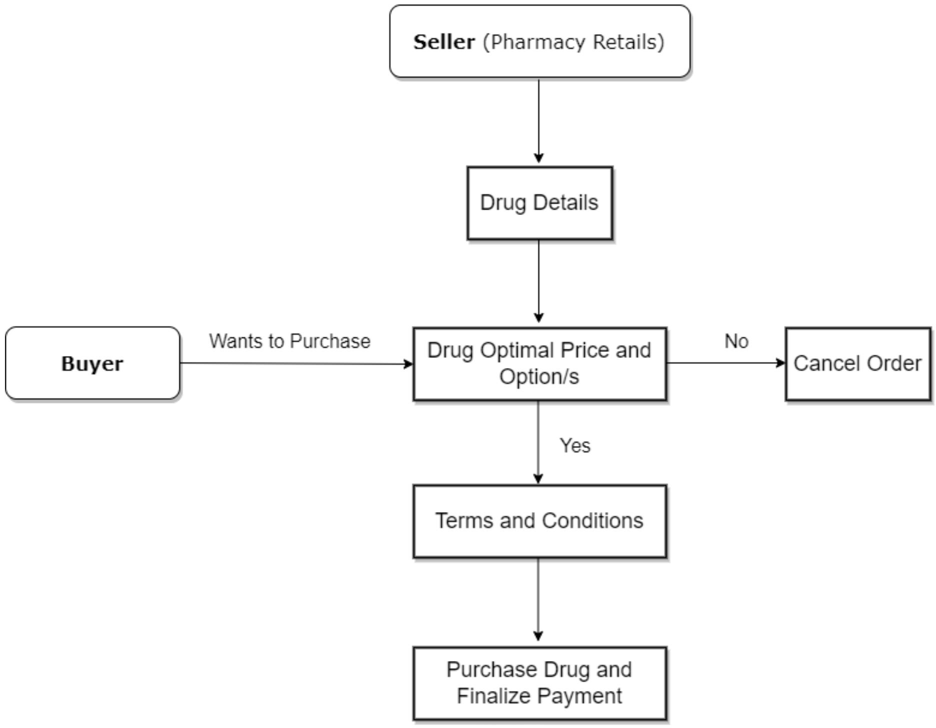


Fig. 5.5 Marketplace Workflow.

The marketplace has an intelligent decision making ability which provides recommendations on the optimal price to sell drugs. The generated recommendations are based on the following factors: the previous price point for which the drugs were sold, the number of other similar drugs being sold in PharmaBlock and the number of persons who are viewing the advertisement. The price prediction module in the marketplace takes as input these multiple factors and provides recommendations on the optimal selling price. There are two steps in setting up the marketplace:

- **Building up the marketplace:** We build a marketplace-based blockchain, where if someone wants to sell a drug, we can create a new block that is referenced or linked to the original blocks and then copy and store drug information from the original blocks. This sets it up as a transaction in the marketplace and every selling transaction that takes place in the marketplace creates a block that is linked to the original source information.

- **Data exchange:** A decentralized marketplace uses blockchain as an enforcer of rules and also as a trusted party between sellers and buyers. Obviously, the drug marketplace consists of two main players, buyers and sellers, both of whom must have public and private keys to exchange data securely and to match sellers with buyers. Additionally, smart contracts are used for sharing data in the marketplace to ensure the privacy of buyers and sellers and also to ensure their authority and level of access to information in the blockchain.

5.6 Modelling an intelligent approach that helps manufacturers to predict future demand for drugs (Req: 4)

A model is developed to predict and compute the number of drugs required to meet the future demand using machine learning predictive models to help manufacturers produce the appropriate number of drugs. This number is based on the number of previously wasted drugs in a certain area taking into account the population growth.

Based on the drug demand over a recent period of time, we predict the number of drugs that will be needed in the future, as shown in Figure 5.6 and we train our model by providing the following data:

- Sequential periods of demands as input.
- Average of population increase per-period as input.
- Total number of wastage statistics as input.

- Total number of SKU drugs to be produced based on the past demand as output.

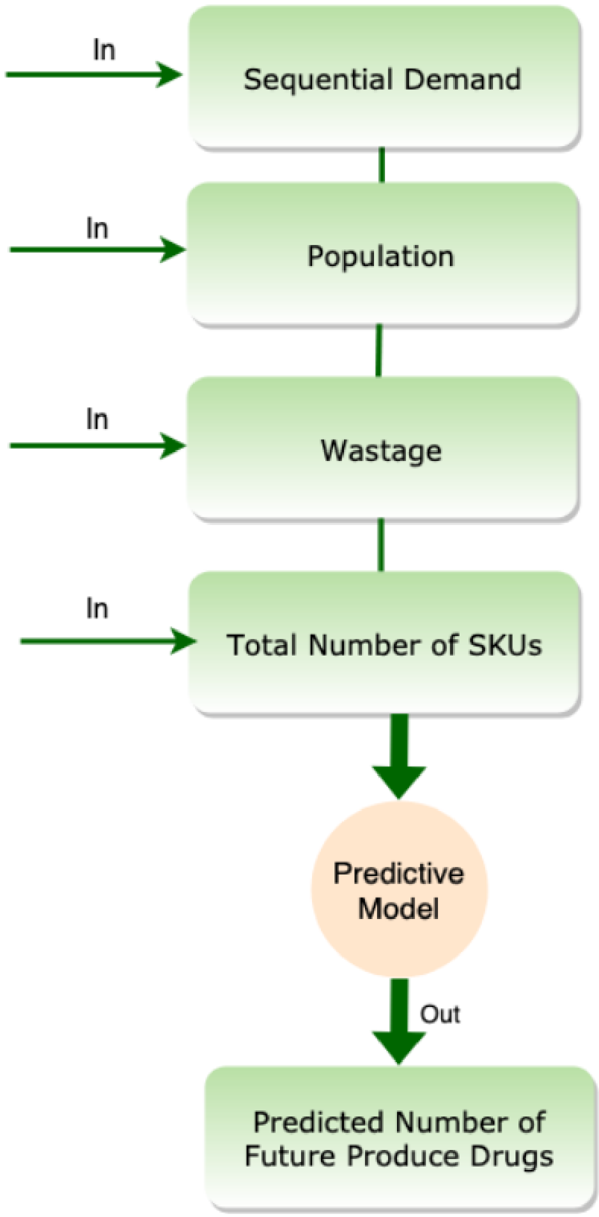


Fig. 5.6 Future Drug Demand Predictive Module.

In our intelligent system, the predictive analytical model will intelligently compute the future demand for drugs. To achieve this goal, we use data from the large manufacturers and form an Intelligent Rule Engine and data from the marketplace such as the population growth as input and then the data is processed using the best performance predictive model. As output, we look to reduce the wastage of drugs by determining the optimal number of drugs that will be required for future use.

5.7 Conclusion

This chapter has proposed *PharmaBlock* intelligent platform framework. This framework addresses all the key requirements of the pharmaceutical supply chain. This proposed framework represents the first attempt to address the issues associated with allowing different levels of access to sensitive data in a pharmaceutical supply chain. It is also the only approach of its type that proposes a date-based alert system. It also includes innovative AI-based algorithmic on top of the blockchain layer to carry out reliable trust for data in PharmaBlock platform.

The next chapter discusses the steps involved in developing an EWD model to alert pharmacies to nearly expiring drugs.

Chapter 6

Early Warning Detection System Proposed Model

6.1 Introduction

In this chapter, the process of generating early warning alerts is discussed. This chapter first presents the three phases in creating the framework and an intelligent model is proposed to alert pharmacies and pharmacy retailers of what medicines they have stock and need to be sold. This combination provides a complete solution to research question 2. This chapter also present the results of the validation and implementation of the proposed solution to research question 2. We created a blockchain-based alert system to answer this research question and used the following to test the system:

1. **Blockchain:** is a distributed digital network that is mainly used for recording transactions across multiple nodes [10]. For our purpose, we use a permissioned parent-child chains for storing the pharmaceutical supply chain data.

2. **Eclipse:** is a free software and it is available and open source tool that serves as an integrated development environment (IDE) for creating Java applications. It includes a core workspace and a customizable plug-in system to tailor the environment to specific needs. In our proposed solution, we utilize this software

to develop a web application that interfaces with the *PharmaBlock* permissioned blockchain using the Apache HTTP Server [87].

3. **RapidMiner:**is a visual data science workflow designer accelerating the prototyping validation of models. The RapidMiner platform provides a comprehensive range of data preparation and machine learning features that can make a significant impact on businesses and projects [88].

This chapter is organized as follows. In Section 6.2, we outline the phases of the date-based early warning system. In Section 6.3 we describe our prototype system implementation and the aim of engineering this prototype. In section 6.4, we discuss our early warning system model and design the workflow for validating the proposed framework. In Section 6.5, we outline and explain the dataset used for validation purposes. In Section 6.5, we explain in a step-wise manner the detailed working of the system prototype. In Section 6.7 we discuss the results obtained from the evaluation. Finally, section 6.8 concludes this chapter.

6.2 Date-based Detection System Framework

In this section, we present our intelligent alert system mechanism to generate alarm notifications to alert pharmacists about the expiry date of drugs using supervised machine learning. To present the end user with intelligent and bespoke time-based alarms alerting them about drug expiry, we propose an early warning system. The date- based early warning system (DBEWS) provides alerts and makes recommendations before the case starts [86]. The fundamental requirements of the Date-based Early Warning System are:

– Automatic detection of all drugs stored in the blockchain using information such as drug expiry date, number of batches and their location.

– Automated indication in the form of alerts to be sent to the pharmacy retails when needed.

The EWS has three phases to generate alerts to warn end users against the impending expiry of drugs, namely the permissioned ledger phase, the execution phase, and the response action phase. These phases are detailed as follows:

6.2.1 Phase 1: Activates the Date-based Early Warning

In this phase, only approved members whose membership has been verified by miners can access the details related to every registered drug in PharmaBlock. The assets on the PharmaBlock platform are drugs, raw material, and orders. In this phase, each user (pharmacy retailers) are provided with a client application interface to easily perform transactions and set up their personalized alert date and time for the drugs they have. At this stage, we set up a timeline that uses a personalized variable value for generating alerts to a pharmacy, where every end-user sets their preferred time window. This personalized variable value generates alerts which vary from pharmacy to pharmacy to let the pharmacy retails know when drugs will expire to ensure these drugs are released onto the marketplace prior to expiry. All drug data is copied to the data cloud storage, which is a tool based on Ardor blockchain. Ardor has a separate data library and can be used for data analytics. The main purpose of copying drug information to the data cloud storage is to analyse these data and apply our machine learning and recommendation system module. We also use this data cloud for the machine learning module and the machine learning recommendation system.
The relationship between all the participants in this phase are describe in Figure 6.1

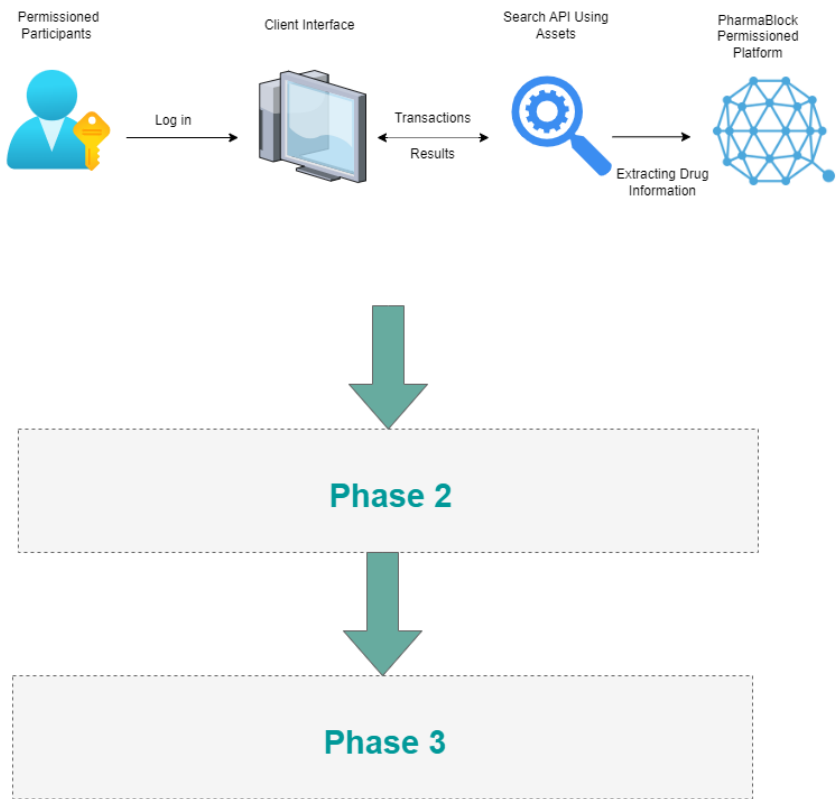


Fig. 6.1 An Overview of Extracting Data of Drugs

6.2.2 Phase 2: Execution The Intelligent Date-Based Early Warning System

Phase two extracts the drug information from the PharmaBlock permissioned blockchain layer, then analyses the drug information to send alerts to pharmacies if these drugs will expire in a certain period of time depending on the personalized value entered by pharmacy retails. The aim of the DBEWS is to remind pharmacy retailers of the drugs which have nearly expired using a proactive solution so they can obtain a benefit by selling these drugs instead of throwing them away. This work is the first to use a DBEWS in pharmaceutical supply chain management. This model takes this variable value and compares it against the expiry of the drug batch; if it is within that, an alert or a recommendation is automatically generated and sent to the end user.

In this phase, Pharmablock uses the intelligent DBEWS algorithm to find nearly expired drugs using the personalized value to identify when to generate alarms.

Figure 6.2 shows our execution flowchart. The execution process can be divided into the following steps:

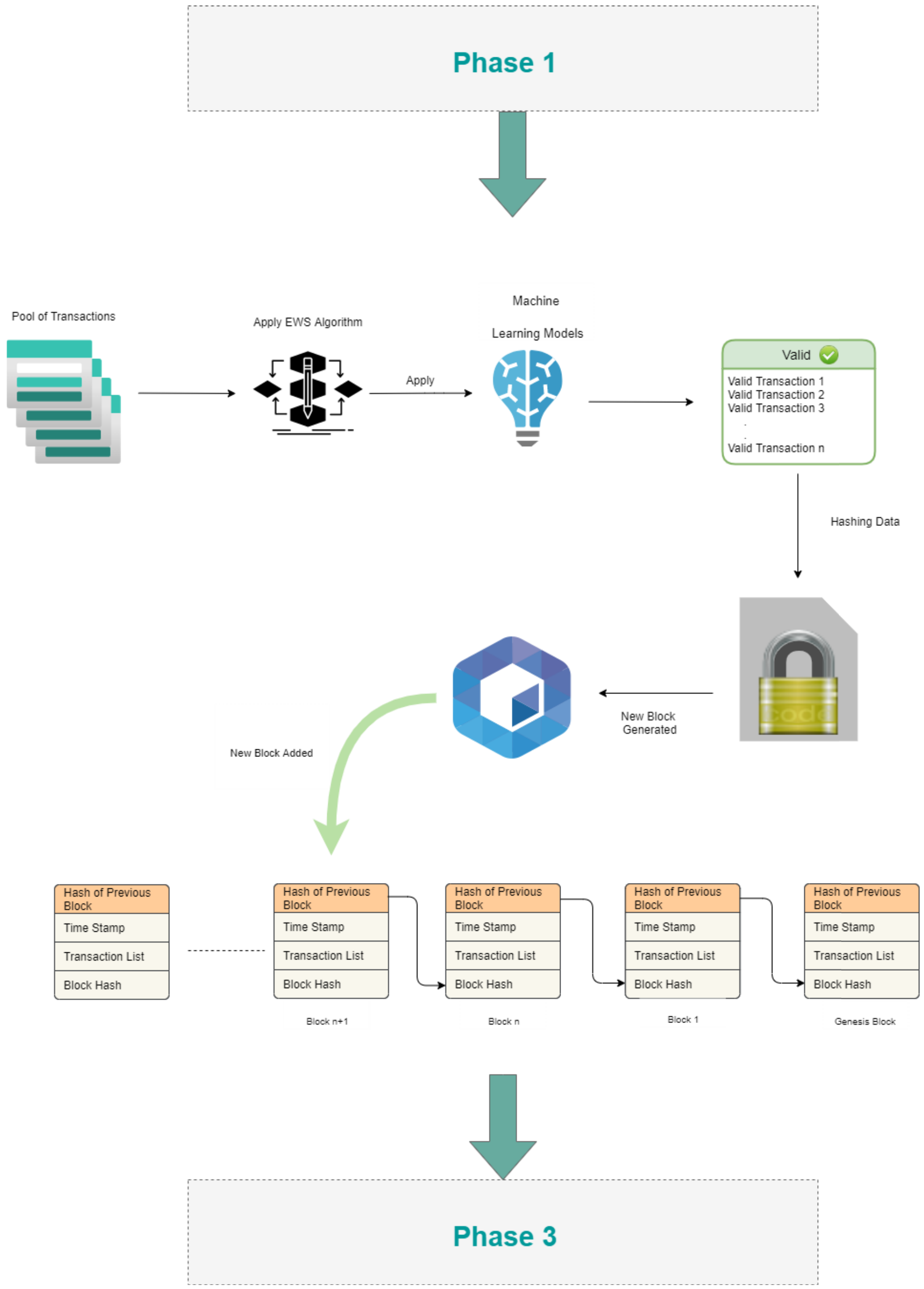


Fig. 6.2 An Overview of the Execution of Drug Data

- **Step 1:** V is the initialization and entering new preferred value of each user.

- **Step 2:** R is for repeating the process for each drugs in PharmaBlock.

– **Step 3:** A is for generating and sending alerts.

– **Step 4:** Execution of our propose algorithm by comparing Variable V against the expiry of the drugs batch and move to the next step.

– **Step 5:** If value V within the expiry date, then alarms automatically generate and send.

– **Step 6:** If value V with out the expiry date, then send a recommendation and repeat step 5.

Algorithm 6.1: An EWDM algorithm

Begin
Store V in the Blockchain
Repeat for every batch in the Blockchain
Compare V with Current date
if $V >$ *current date value* **then**
    EWDM (V, R, A)
else
    Generate an alert A
else
    Send a recommendation
Stop

6.2.3 Phase 3: Generating and Sending Alerts to the Client

Once phase two has been executed, EWS generates a transaction on PharmaBlock and sends a notification to the clients, informing them of the drug expiry date and the importance of disposing of these drugs to other pharmacies, hospitals and customers and making some recommendations on ways to dispose of them.

The work of the EWS relates to the next two objectives of this research. The general working of this phase is illustrated in Figure 6.12

Once the input preferred value is equal to the current date, an alarm is generated using the PharmaBlock web server, otherwise a recommendation to safely dispose of the drugs will be sent through the server. The PharmaBlock web server sends alerts to the client whenever value V = to the current date.

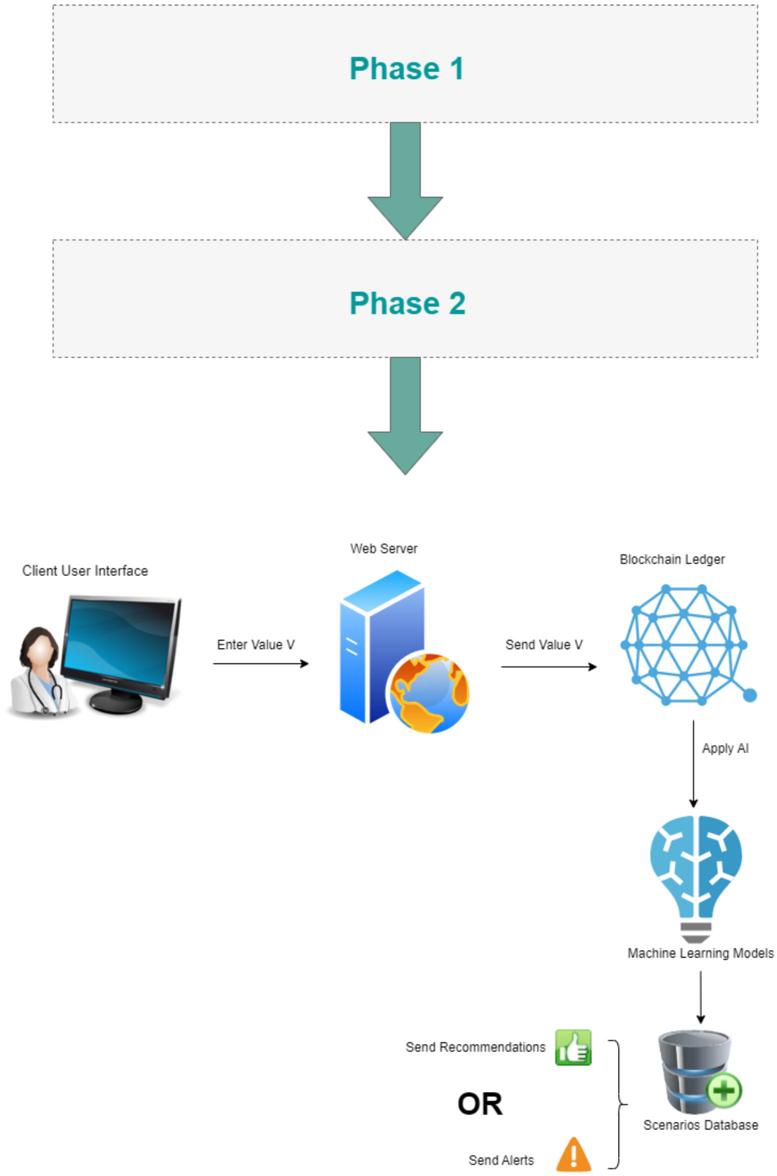


Fig. 6.3 An Overview of Sending Feedback to the Clients

6.3 Prototype System Implementation

6.3.1 Aims of Engineering the Prototype System

The main goal of developing the prototype system is to simulate the functionality of the PharmaBlock Service, which is a smart contract executing framework built on Ardor. The purpose of this section is to utilize the PharmaBlock prototype to assess the effectiveness of the methods suggested in the previous section for storing alerts and generating alarms. To validate the other objectives of this thesis, the prototype system was further enhanced (see Chapter 7 and Chapter 8).

As discussed in Chapter 2, in the current literature and also in practice, one of the major challenges of pharmaceutical supply chain systems is the wastage associated with a large number of expired drugs. With our intelligent framework which involves the integration of smart contracts and predictive models, pharmacy retailers can now take effective action in relation to nearly expiring medicines.

We used the Ardor blockchain technology as our computing platform and its programming language is Java. We set up the environment using IntelliJ IDEA to run the Ardor server and deploy smart contracts. However, Ardor blockchain is in the development stage. Hence, it was not possible for us to use any other platform other than Ardor which supports child chaining.

6.4 Modelling and Designing the Date-based Detection Web Server(Services)

This section details how we model the PharmaBlock web server and connect it to the blockchain platform to allow every client to communicate easily with PharmaBlock.

6.4.1 Workflow for Solution

To achieve the second aim of this research, we modeled our client web application using Eclipse IDE. To deploy our web services, Eclipse requires that an application server is configured for its use. For this, we used the Apache Tomcat open source application server.

Several components collaborate to allow the date-based early warning system works. The following steps present the workflow of the process in detail.

- **Step 1:** set up *The Child Chain Control* feature to give platform users the ability to control who can perform transactions on the child chain. For example, FDA and the MASTER ADMIN of large manufacturers can give permission to pharmacy retailers to access the web application to set up their preferred day and time to send alerts for each batch of drugs.

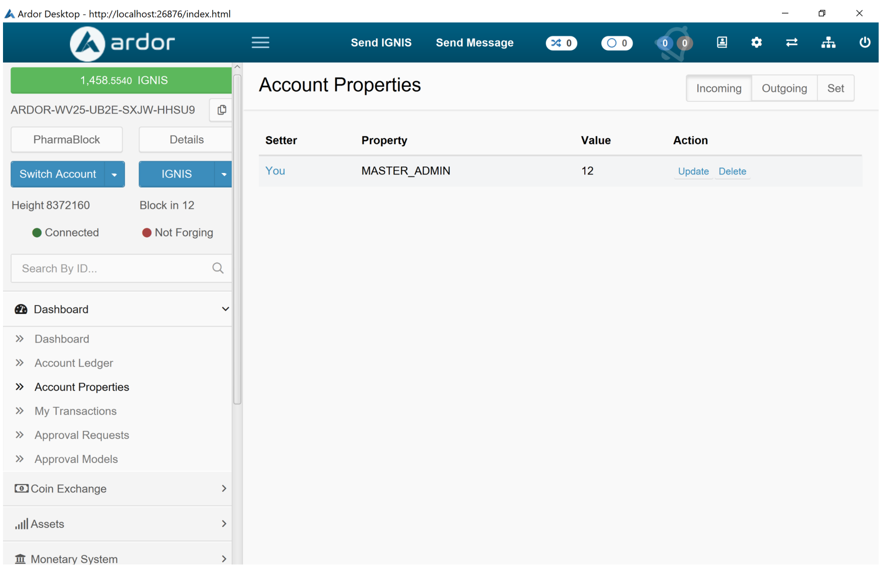


Fig. 6.4 Screenshot of the Configuration Set-up for MASTER ADMIN Permissioned Control

- **Step 2:** MASTER ADMIN can divide the other users into two types: CHAIN ADMIN and CHAIN USER. CHAIN ADMIN nodes can only access the web application and set their time window.

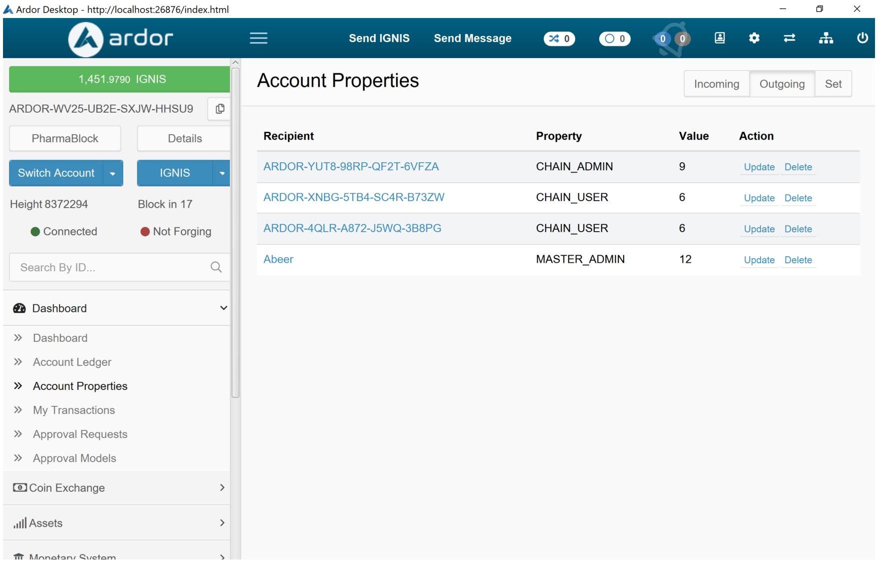


Fig. 6.5 Screenshot of the Configuration Set-up for the Control of Multiple Permissioned Accounts


```
{
    "hasPermissions": [
        {
            "accountRS": "ARDOR-XNBG-5TB4-SC4R-B73ZW",
            "granterRS": "ARDOR-2222-2222-2222-22222",
            "permission": "MASTER_ADMIN",
            "granter": "0",
            "account": "11420043567262781742",
            "height": -1
        }
    ],
    "hasEffectivePermissions": [
        {
            "accountRS": "ARDOR-XNBG-5TB4-SC4R-B73ZW",
            "granterRS": "ARDOR-2222-2222-2222-22222",
            "permission": "MASTER_ADMIN",
            "granter": "0",
            "account": "11420043567262781742",
            "height": -1
        }
    ],
    "canGrantPermissions": [
        "CHAIN_ADMIN",
        "BLOCKED_CHAIN_ADMIN"
    ],
    "requestProcessingTime": 5
}
```


Fig. 6.6 Sample of JSON File Response for Obtaining Account Permission

```
{
    "signature": "4a6b516fd3f95ff027d607f7529d5cabf6a3a13dca74292cd0b13fc0
06d37d0e179ef3204d536a91f22ac9b0cdc7cffc2834bbd04a30268820edeb089a687fca",
    "transactionIndex": 1,
    "type": 10,
    "fxtTransaction": "6157199982548781174",
    "phased": false,
    "ecBlockId": "17538382732075311219",
    "signatureHash": "b02c3a7b533930f8f28b827a9c8197bbe86cc1fabdebd7e621ca
2788c288b297",
    "attachment": {
        "property": "CHAIN_USER",
        "value": "6",
        "version.AccountProperty": 1
    },
    "senderRS": "ARDOR-WV25-UB2E-SXJW-HHSU9",
    "subtype": 1,
    "amountNQT": "0",
    "recipientRS": "ARDOR-4QLR-A872-J5WQ-3B8PG",
    "block": "15269544578721901182",
    "blockTimestamp": 117281890,
    "deadline": 15,
    "timestamp": 117281874,
    "height": 8372264,
    "senderPublicKey": "6619ea44f4be00056c07d63a248c4f43ed18fc3710fe57989d
b53f81ee81961e",
    "chain": 2,
    "feeNQT": "25000000",
    "requestProcessingTime": 1,
    "confirmations": 296,
    "fullHash": "06c5183637494628f4769e17a927cf4198533d6ff744acf942d52406b
7df8352",
    "version": 1,
    "sender": "17576159366448311299",
    "recipient": "1681189844241439319",
    "ecBlockHeight": 8371542
}
```


Fig. 6.7 Sample of JSON File Response for Confirming an Account Permission Control

– **Step 3:** all the values entered by CHAIN ADMINS are stored in a permissions table using a local database on the chain admins' devices using the MySQL database with a row for each user.

– **Step 4:** once the CHAIN ADMIN enters the preferred time and date, a transaction is automatically generated on the PharmaBlock platform.

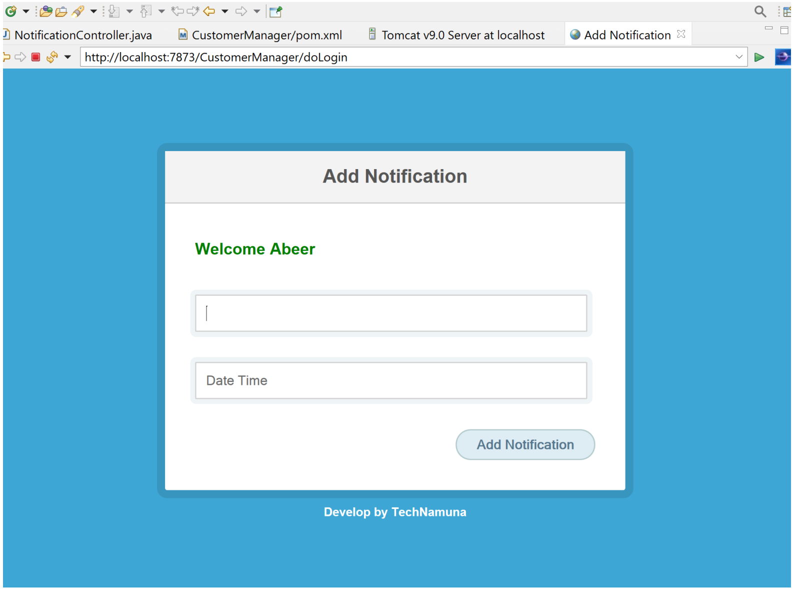


Fig. 6.8 Screenshot of Login into the PharmaBlock Web Application

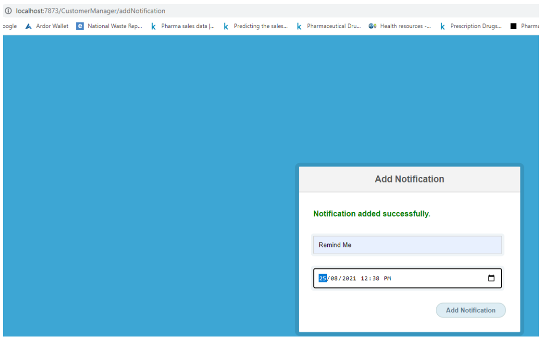


Fig. 6.9 Screenshot of Storing Date and Time into the PharmaBlock Web Application

- **Step 5:** The intelligent date-based algorithm checks whether to react, depending on multiple factors.
- **Step 6:** a valid block will be added to the child chain once an alarm or a recommendation is sent to the CHAIN ADMIN.

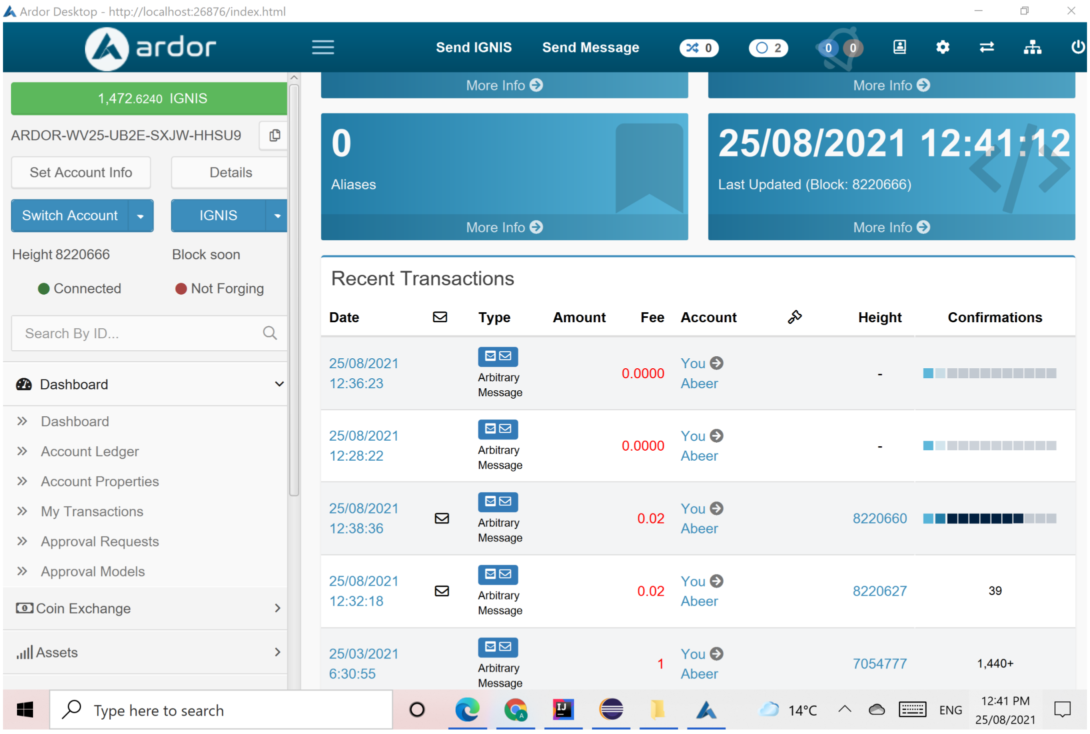


Fig. 6.10 Screenshot of Adding a New Block to the Permissioned Chain

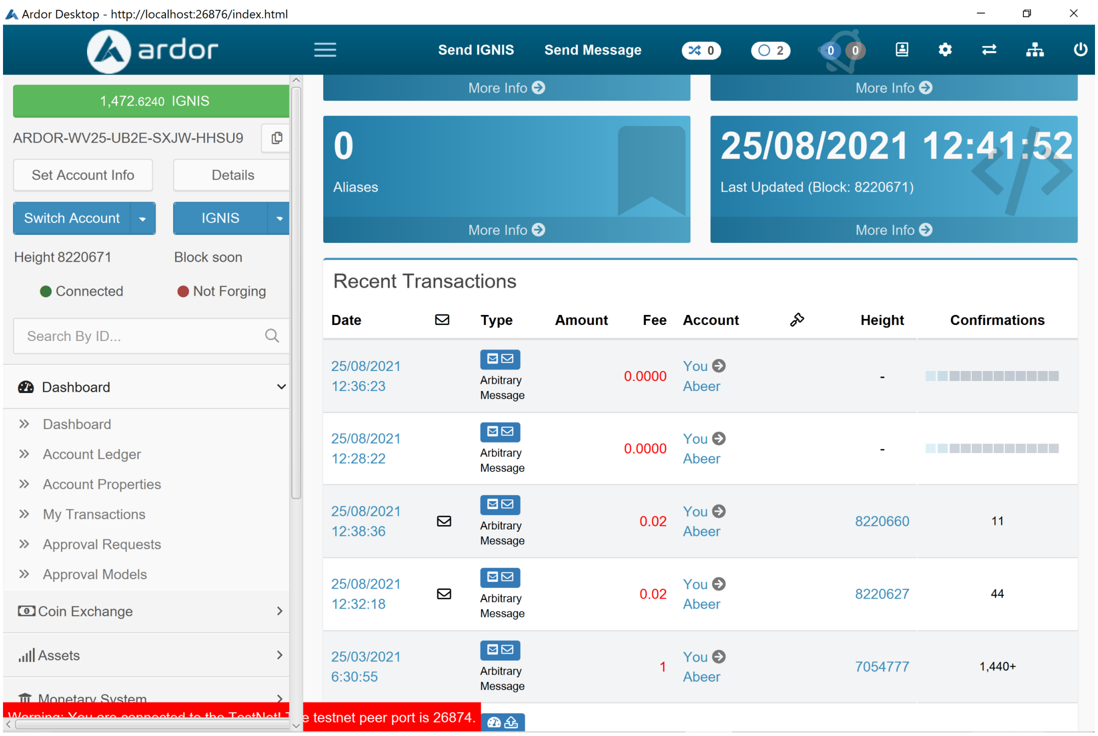
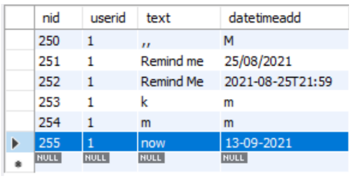


Fig. 6.11 Screenshot of a Confirmed Block Added to the Permissioned Chain

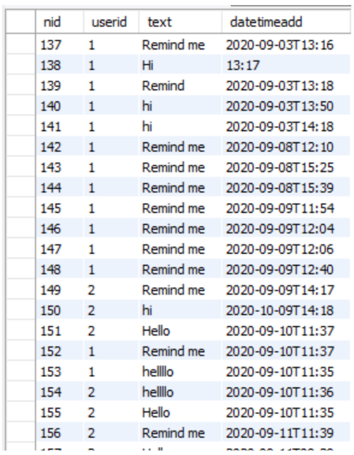
6.5 Dataset Used for Validation

The dataset we built and linked to our web application using the MySQL database is used for validation. We define permissioned users with a username and host name to access the MySQL database. The data is real and we set multiple permissioned users who can assign multiple batches of drugs with the set date and time to generate alerts for each batch. A screenshot of the dataset are listed below 6.12 and 6.13.



nid	userid	text	datetimeadd
250	1	,,	M
251	1	Remind me	25/08/2021
252	1	Remind Me	2021-08-25T21:59
253	1	k	m
254	1	m	m
255	1	now	13-09-2021
NULL	NULL	NULL	NULL

Fig. 6.12 Screenshot of the Permissioned Database



nid	userid	text	datetimeadd
137	1	Remind me	2020-09-03T13:16
138	1	Hi	13:17
139	1	Remind	2020-09-03T13:18
140	1	hi	2020-09-03T13:50
141	1	hi	2020-09-03T14:18
142	1	Remind me	2020-09-08T12:10
143	1	Remind me	2020-09-08T15:25
144	1	Remind me	2020-09-08T15:39
145	1	Remind me	2020-09-09T11:54
146	1	Remind me	2020-09-09T12:04
147	1	Remind me	2020-09-09T12:06
148	1	Remind me	2020-09-09T12:40
149	2	Remind me	2020-09-09T14:17
150	2	hi	2020-10-09T14:18
151	2	Hello	2020-09-10T11:37
152	1	Remind me	2020-09-10T11:37
153	1	helllo	2020-09-10T11:35
154	2	helllo	2020-09-10T11:36
155	2	Hello	2020-09-10T11:35
156	2	Remind me	2020-09-11T11:39

Fig. 6.13 Screenshot the Permissioned Database

6.6 Working of the Prototype System

The PharmaBlock platform carries out the computations at two levels, namely local computations and blockchain computations. For the local level computations, all the values are stored and executed locally. For our proposed DBEWS, computation processing occurs locally. However, all values are copied in the blockchain platform. All steps for both computation levels are presented in Section 6.6.1 and Section 6.6.2.

6.6.1 Steps in Local Devices

After a new date and time have been submitted through the PharmaBlock web application, the values are stored and executed as shown in Figure 6.14 and are described as follow:

- Step 1: The local web application gets the new value for all items and stores it in MySQL locally.
- Step 2: Copy all values and link them to the drug information that is stored in PharmaBlock.
- Step 3: Execute the DBEW algorithm in the local machine to predict which day and time to send notifications or when to send recommendations.
- Step 4: Send the prediction results back to the PharmaBlock platform.
- Step 5: Execute the action required by sending alerts or recommendations.

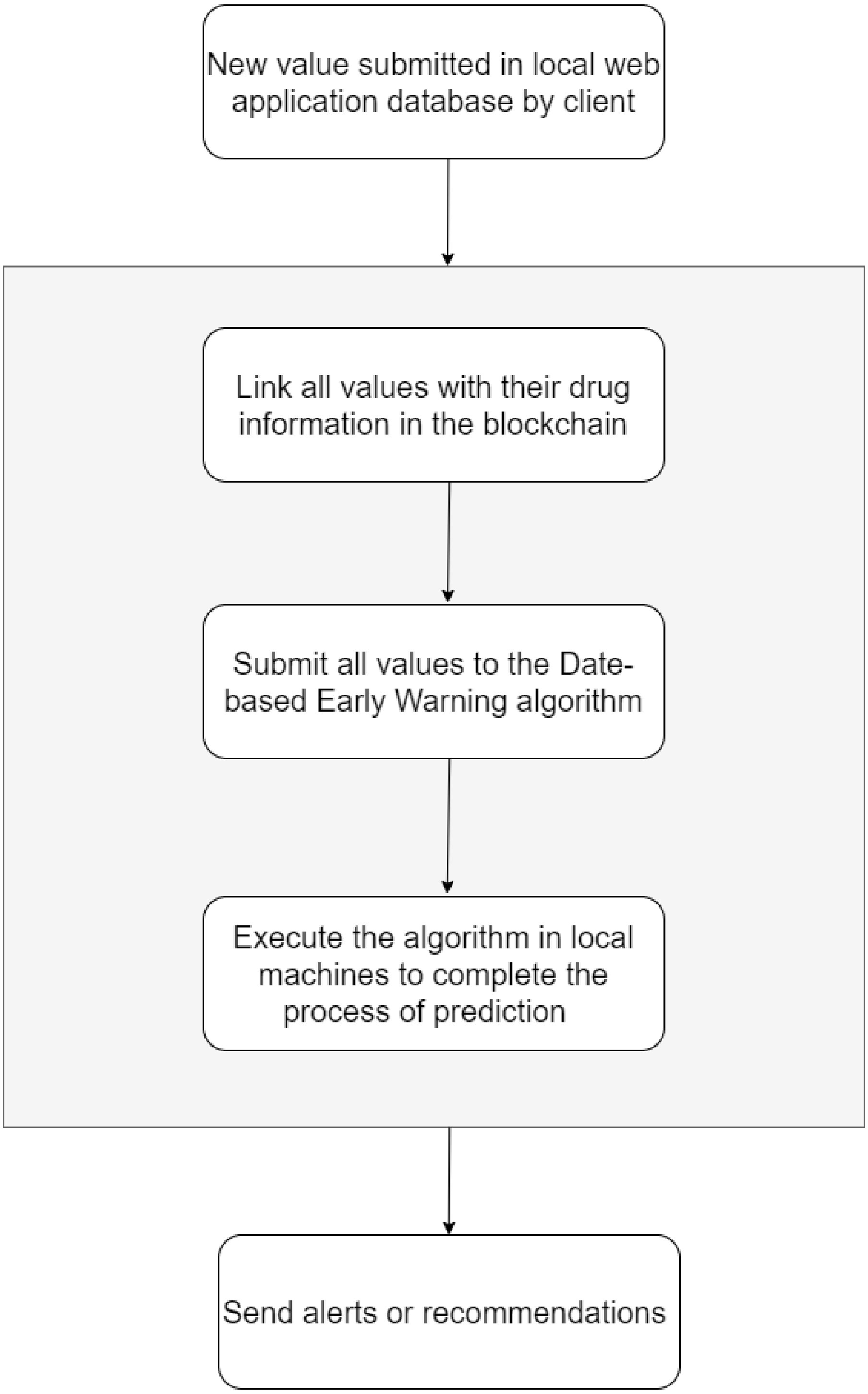


Fig. 6.14 Flowchart of Computing the Value of the Date-Based Algorithm

6.6.2 Steps in PharmaBlock Blockchain

After the new date and time values are predicted by the Date-based Early Warning algorithm locally as shown in Figure 6.15 and are described as follow:

- Step 1: PharmaBlock receives a copy of the values entered.
- Step 2: The values are stored in the Ardor data cloud using smarts contracts.
- Step 3: A new block is generated once a notifications is sent or a recommendation is sent to the client.

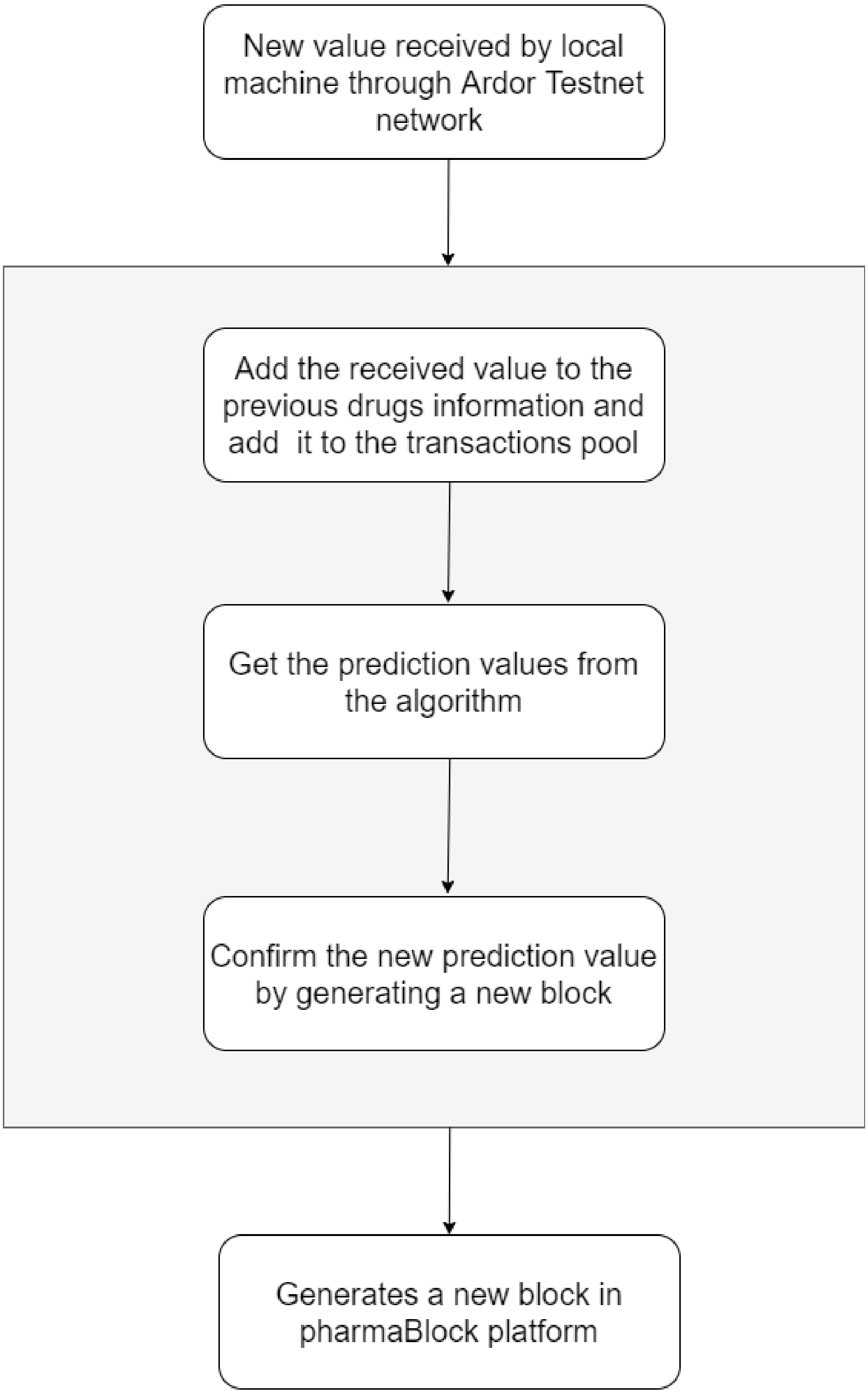


Fig. 6.15 Flowchart of the PharmaBlock Computation Process

6.7 System Evaluation, Results and Discussion

6.7.1 Prototype Evaluation

In this section, we present our mechanism for predicting the alarms which should be generated to notify the pharmacists prior to drug expiry using supervised learning as shown in Figure 6.16.

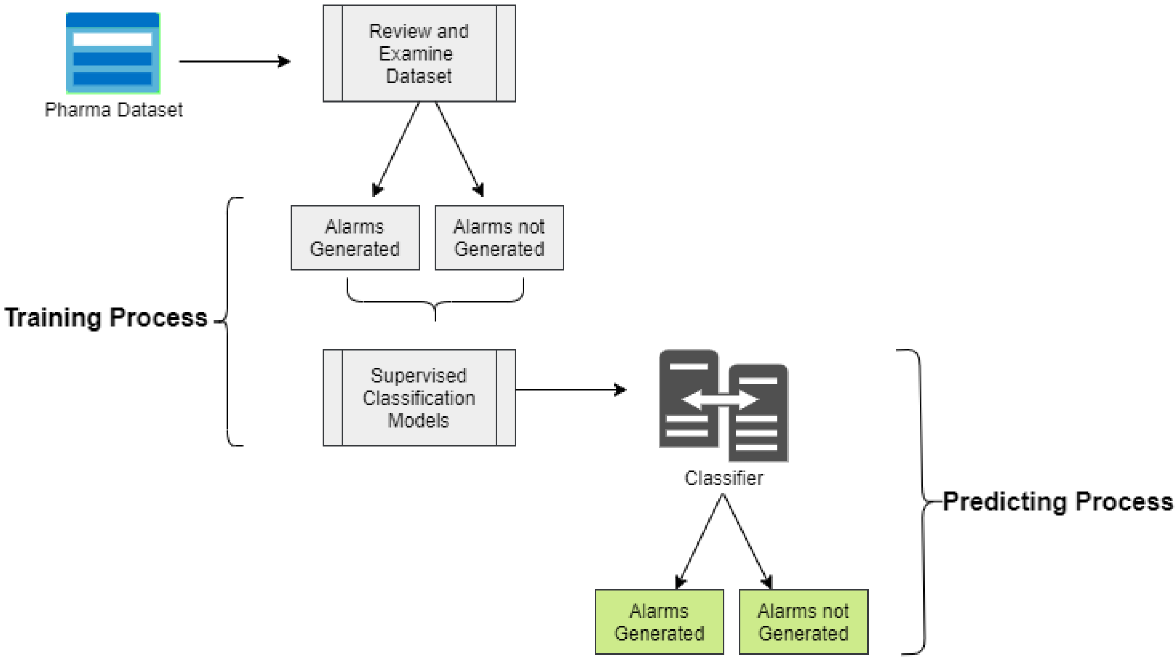


Fig. 6.16 The Experiment Framework for EWS

Our model consists of three phases: collecting data and preparing the dataset, the training process, and the predicting process. First, we collected the information from our PharmaWeb server. The dataset consists of several columns, namely Drug-Name; User-ID; Notifications; Drug-Expiry-Date. The dataset also consists of 1000 records with multiple users. Then, we examined the dataset manually to ensure the quality of the data. We also captured the generated alarms and documented them manually. Second, we trained different algorithms using the training dataset using the Drug-Expiry-Date as input. Finally, we tested our models for the evaluation and to examine their ability to predict.

In this experiment, we applied six supervised algorithms, namely generalized linear regression, logistic regression, deep learning, decision tree, support vector machines, and naive Bayes model. A brief description of each algorithm follows:

1. ***Generalized Linear Model / classifier***

   The generalized linear model (GLM) differs from other models due to its ability to test a non-linear model in the context of regression. GLM is a mathematical framework and is a supervised classifier mechanism. This model is widely used because of its natural approximation for complex functional relationships and is straightforward in terms of estimating the unknown parameters [89]. In this study, we applied the GLM to our dataset using the RapidMiner platform and the performance of this model as detailed in Tables 6.1 - 6.5. The expected output is a classifier model that will identify the exact time to generate the alarms from others.

2. ***Logistic Regression / classifier***

   The logistic regression model is used for binary classification problems (two-class values). The logistic regression model is widely used in medical fields to predict mortality in injured patients. This model has many diverse areas of application as described in [90]. In this study, we use the logistic regression model using RapidMiner to divide the dataset output into two groups of predictions which tells us if the alarm has been generated at the predicted time. The performance metrics of this model are detailed in Tables 6.1 - 6.5.

3. ***Deep Learning / classifier***

   A deep learning model is essentially a neural network with three or more layers and is a classifier that is well trained and can extract features from a large group of examples to assign labels to textual units. This model has been proven to be powerful in mimicking human skills. It has a wide range of applications such as those detailed in [91]. In this study, the deep learning algorithm is used for text classification, and we designed and applied the deep learning model in

RapidMiner to build the classifier. The performance metrics results of this model are shown in Tables 6.1 - 6.5.

4. ***Decision Tree / classifier***

   The decision tree algorithm starts with a root node at the top, which splits the dataset into smaller branches to form a decision tree structure. This method is commonly employed for data mining and text classification, as demonstrated in the examples provided in [92]. In this thesis, we use the decision tree algorithm to build a model to predict the time to generate the notification for pharmacy retailers. We implement our model using the SVM operator in the RapidMiner Platform and the output is a classifier model that will help in determining when the future notification will be sent. The performance metrics results of this model are shown in Tables 6.1 - 6.5.

5. ***Support Vector Machine Model/ classifier***

   The support vector machine (SVM) algorithm is a popular text classification model known for its effectiveness across various domains. Initially developed for binary classification in [93] for binary classification. It has since been successfully applied to several other applications, as discussed in [94]. In this study, the linear support vector machine algorithm is used for text classification and we used the SVM model in RapidMiner to build the SVM classifier. To train and test the classifier, we divided the dataset into two classes. The performance metrics results of this model are shown in Tables 6.1 - 6.5.

6. ***Naive Bayes Model / classifier***

   The naive Bayes classifier is frequently utilized for text classification in various fields. It is a straightforward probabilistic classifier that employs Bayes' theorem to anticipate the class of a new document [95]. Unlike other classifiers, a naive Bayes model is efficient because it only necessitates a small training dataset to approximate the output [96]. In this research, we implemented the naïve

Bayes model using the naïve Bayes operator in the RapidMiner platform. The performance metrics results of this model are shown in Tables 6.1 - 6.5.

Generalized Linear Model	96.9%
Logistic Regression Model	90.8%
Deep Learning Model	98.5%
Decision Tree Model	100.0%
SVM Model	92.3%
Naive Bayes Model	92.3%
Overall Accuracy = 95.1%	

Table 6.1 Accuracy Overall

Generalized Linear Model	3.1%
Logistic Regression Model	9.2%
Deep Learning Model	1.5%
Decision Tree Model	0.0%
SVM Model	7.73%
Naive Bayes Model	7.7%
Overall Classification Error = 4.8%	

Table 6.2 Classification Error Overall

Generalized Linear Model	96.9%
Logistic Regression Model	96.9%
Deep Learning Model	100.0%
Decision Tree Model	100.0%
SVM Model	92.3%
Naive Bayes Model	92.3%
Overall Precision = 96.4%	

Table 6.3 Precision Overall

Generalized Linear Model	100.0%
Logistic Regression Model	93.6%
Deep Learning Model	98.5%
Decision Tree Model	100.0%
SVM Model	100.0%
Naive Bayes Model	100.0%
Overall Recall = 98.6%	

Table 6.4 Recall Overall

Generalized Linear Model	98.4%
Logistic Regression Model	95.0%
Deep Learning Model	99.2%
Decision Tree Model	100.0%
SVM Model	96.0%
Naive Bayes Model	96.0%
Overall F Measure = 97.4%	

Table 6.5 F Measure

6.7.2 Prototype Results and Discussion

We designed an "on-the-fly" date-based early warning system according to the experiment framework in Figure 6.16. Additionally, to conduct supervised machine learning, we built our dataset using the RapidMiner platform. We conducted 2-fold cross-validation in this experiment, meaning the data is divided into two groups, one being the training set and the other being the test set. We used six approaches to predict the date to generate the notification based on the drug expiry date on our PharmaWeb Server. To evaluate our model, we used multiple evaluation metrics namely accuracy, classification error, precision, recall and F-measure for each approach, Tables 6.1 - 6.5 detail the performance of each approach. Class recall and precision refer to the recall ratio and precision ratio of the generated warnings respectively. Accuracy is the most commonly used metric to assess classifier efficiency. Overall accuracy indicates the total number of the alarms that were correctly generated as a percentage of the total numbers of the alarms generated [97]. Accuracy in Table 6.1 indicates the overall accuracy of the different approaches. We also used the F-measure metric to measure how accurate our model is when applying different approaches. The classification error in this study tells us the number the alarms that were not successfully generated on time or were not generated at all. We conducted the experiment and the results show that the decision tree model achieved the best performance over the other classification models, whereas the logistic regression model achieved the worst performance.

6.8 Conclusion

In this chapter, we discussed all the phases that comprise the DBEWS framework. In particular, we discussed in a step-wise manner the processes involved in the activation of the early warning system phase, the execution phase and the generating and sending alerts phase. In addition, we proposed a model to collect all reminders by customers using the permissioned blockchain. This solution was developed to address the second research objective of this thesis.

In this chapter, we also proposed a simulation framework for validating the solution to research objective 2. This was done using a real dataset collected by our PharmaBlock Web Application. At the end of the validation and implementation process, the results show that our proposed model is able to generate and send alerts accurately.

The next chapter discusses the steps involved in developing a decentralized marketplace to sell nearly expire drugs for an optimal price.

Chapter 7

Proposed Decentralized Marketplace Model

7.1 Introduction

In this chapter, the process of extracting information on about-to-expire drugs using the proposed framework is discussed. This introduction presents the three phases involved in creating the framework and also proposes an intelligent model to predict the most optimal price at which to sell over-the-counter medications that are about to expire. This proposed solution will help pharmacies and pharmacy retailers know what medicines they have in stock which need to be sold before they expire, providing a complete solution to research question 3. This chapter also presents the results of the validation and implementation of the proposed solution to research question 3. We created an intelligent decision-making centre which provides recommendations on the optimal price to sell nearly expired drugs, based on multiple factors to answer this research question and we used the following to test the system:

1. **Blockchain:** is a distributed digital ledger which is used for recording transactions across different multiple nodes [10]. For our purpose, we use permissioned parent-child chains for storing the pharmaceutical supply chain data.

2. **Azure Machine Learning Studio:** is a cloud-based service designed to streamline and expedite the machine learning project lifecycle. It is used by professionals

in the field, such as data scientists and engineers, to train and deploy models [98].

3. **RapidMiner:** is a visual data science workflow designer accelerating the prototyping validation of models. This tool provides a visual data science workflow designer. With the RapidMiner platform, organizations or projects can access all the necessary data preparation and machine learning capabilities to achieve real impact [88].

This chapter is structured as follows. Section 7.2 outlines the phases of the decentralized marketplace workflow. Section 7.3 describes the implementation of the proposed prototype system and the reason for engineering this prototype. Section 7.4 discusses our predictive price model and the design of the workflow to validate the proposed framework. Section 7.5 describes the dataset used for validation purposes. Section 7.6 explains in a stepwise manner the detailed working of the system prototype. Section 7.7 discusses the results obtained from the evaluation. Section 7.8 details the validation of the prototype system framework. Finally, section 7.9 concludes this chapter.

7.2 Workflow of the Proposed Decentralized Marketplace Model in PharmaBlock

In this section, we present the mechanism of selling and buying products in the PharmaBlock platform. Blockchain technology enables sellers and buyers to transact in a trusted environment where the role of a third party is not needed. In this chapter, we present the main purpose of using a decentralized marketplace which displays just-in-time drugs that are close to expiring. The E-marketplace platform is designed for permissioned users only as we only want to deal with authorized information, hence only authorised users who are part of the PharmaBlock platform can provide a listing; however, anyone should be able to make a purchase using a smart contract, meaning both registered and non-registered users (including general consumers and patients) are allowed to use and access this marketplace if they have joined the PharmaBlock platform network. Briefly, the PharmaBlock marketplace is for pharmacy retails to dispose of their nearly expired drugs at an optimal price whenever they wish to sell. The marketplace interacts with the PharmaBlock platform by extracting the basic information required to dispose of the drugs, such as how many batches are available for sale and what is the selling price.

The marketplace has an intelligent decision-making centre which provides recommendations on the optimal price to sell the nearly expired drugs. The generated recommendations are based on the following factors: the previous price point for which the drugs were sold, the number of other similar drugs being sold on the PharmaBlock platform and the number of customers who are viewing the advertisement. The price prediction module in the marketplace takes this input and provides recommendations on the optimal selling price. To facilitate this process, we divide it into three phases which are described in the following sections.

7.2.1 Phase 1: Permissioned users Extract Drugs Information

In this phase, only permissioned users who have been assigned to the PharmaBlock platform as a CHAIN ADMIN can sell products in the marketplace. Once a permissioned user (pharmacy retailer or distributor) has received a warning alerting them that a product is about to expire (described in detail in Chapter 5), the CHAIN USER can access and extract information related to the product which is about to expire from the PharmaBlock platform. More specifically, all the drug data are copied to the data cloud storage which is a tool based on Ardor blockchain. This tool is a decentralized data storage system and a separate data library which can be used for data analytics. The main purpose of copying the drug information to the data cloud storage is to analyse these data and apply our machine learning and predictive model.

7.2.2 Phase 2: Execution of The Predictive Optimal Price Model

After extracting the drug information, the pharmacy retailer or distributor needs to determine the best price to sell this product in the marketplace by applying the price predictive model. In this phase, the information from the data cloud storage is collected as a dataset and sent to the machine learning model to analyse the drug information to predict the optimal selling price to obtain a benefit from the nearly expired drugs and reduce the number of expired medicines which are thrown away.

7.2.3 Phase 3: Display Drugs in the Marketplace

After using the predictive machine learning models, the product, its description, the quantity available, and the optimal price to sell the drug is displayed on the PharmaBlock marketplace product list and is available for any user to purchase. Consumers click on the name of the drug they wish to purchase and specify the quantity needed, delivery deadline (how long the consumer is willing to wait for the seller to deliver the product until the transaction is cancelled), and they can also add notes (optional). Once the order has been placed, a new block is generated and consumers can see the order status.

Figure 7.1 illustrates the working process of the decentralized marketplace.

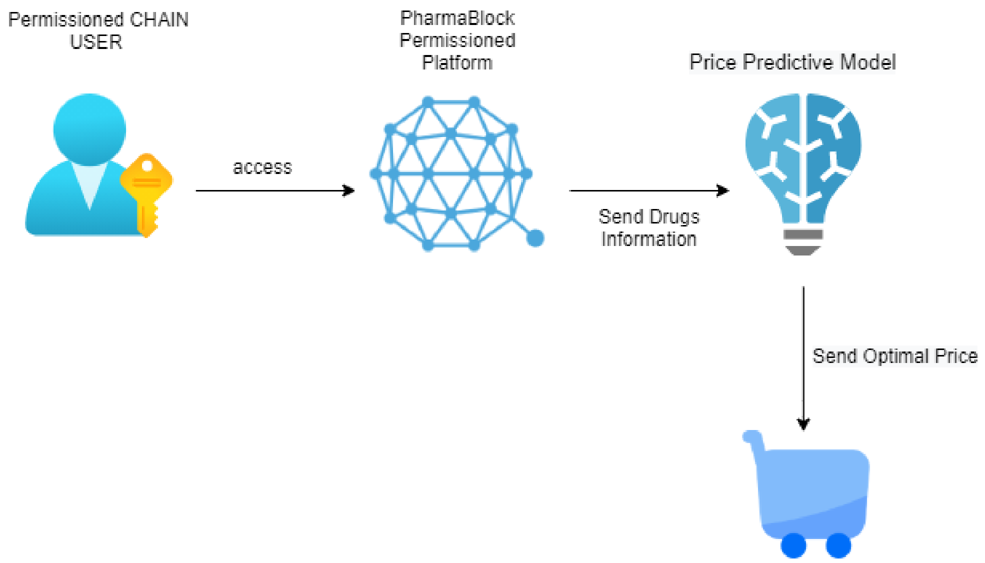


Fig. 7.1 Workflow of Decentralized Marketplace

7.3 Prototype System Implementation

7.3.1 Aim of Engineering the Prototype System

The primary aim of engineering the prototype system is to simulate the working of the PharmaBlock services, an intelligent framework that executes a predictive price model. This section details how the developed PharmaBlock prototype is used to test the efficacy of the methods proposed in the previous section to allow the participant to sell and buy nearly expired drugs for an optimal price. To achieve the other objectives, we extend the prototype system (Chapter 7).

As discussed in Chapter 2, in the current literature and also in practice, one of the major challenges of pharmaceutical supply chain systems is the waste of a large amount of expired drugs. With our intelligent framework which involves the integration of predictive models, pharmacy retailers now can act effectively in relation to stored medicines.

We used Ardor blockchain technology as our computing platform and its programming language is Java. We also set up the environment using IntelliJ IDEA to run the Ardor server and deploy smart contracts. However, Ardor blockchain is in the development stage. Hence, it was not possible for us to use any other platform other than Ardor which supports child chaining.

7.4 Modeling and Designing the Decentralized Marketplace

This section describes how we use the Ardor marketplace and connect it to the PharmaBlock platform to allow every permissioned client to communicate easily with other consumers on the platform.

7.4.1 Workflow for the Solution

To achieve the third aim of this research, we used the Ardor open marketplace but we only specify permissioned users who can sell their products using smart contracts in the PharmaBlock permissioned platform.
Several components collaborate to enable the decentralized marketplace to work. The following steps present the workflow of the process in detail.

- **Step 1:** set up the *The Child Chain Control* feature to give platform users the ability to control who can perform a transaction on the child chain. For example, FDA and large manufacturers MASTER ADMIN can give permission to CHAIN ADMIN like pharmacy retailers and distributors to access the PharmaBlock marketplace to sell the about-to-expire drugs. Figures 7.2 and 7.3 show the configuration permission account control and the JSON file response.

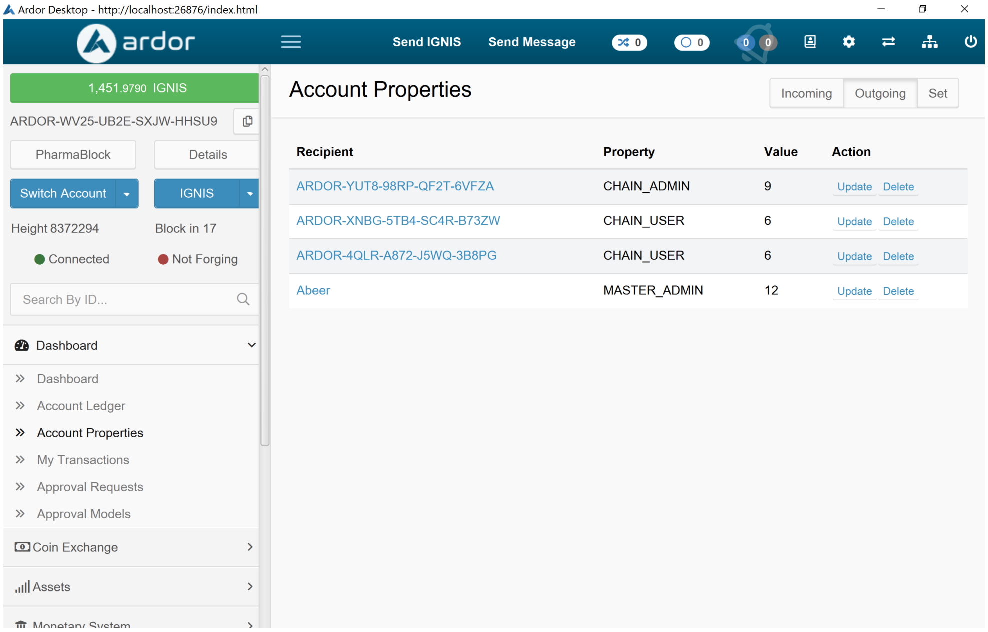


Fig. 7.2 Screenshot of the Configuration Set-up to Control Multiple Permissioned Accounts


```
{
    "signature": "4a6b516fd3f95ff027d607f7529d5cabf6a3a13dca74292cd0b13fc0
06d37d0e179ef3204d536a91f22ac9b0cdc7cffc2834bbd04a30268820edeb089a687fca",
    "transactionIndex": 1,
    "type": 10,
    "fxtTransaction": "6157199982548781174",
    "phased": false,
    "ecBlockId": "17538382732075311219",
    "signatureHash": "b02c3a7b533930f8f28b827a9c8197bbe86cc1fabdebd7e621ca
2788c288b297",
    "attachment": {
        "property": "CHAIN_USER",
        "value": "6",
        "version.AccountProperty": 1
    },
    "senderRS": "ARDOR-WV25-UB2E-SXJW-HHSU9",
    "subtype": 1,
    "amountNQT": "0",
    "recipientRS": "ARDOR-4QLR-A872-J5WQ-3B8PG",
    "block": "15269544578721901182",
    "blockTimestamp": 117281890,
    "deadline": 15,
    "timestamp": 117281874,
    "height": 8372264,
    "senderPublicKey": "6619ea44f4be00056c07d63a248c4f43ed18fc3710fe57989d
b53f81ee81961e",
    "chain": 2,
    "feeNQT": "25000000",
    "requestProcessingTime": 1,
    "confirmations": 296,
    "fullHash": "06c5183637494628f4769e17a927cf4198533d6ff744acf942d52406b
7df8352",
    "version": 1,
    "sender": "17576159366448311299",
    "recipient": "16811898442441439319",
    "ecBlockHeight": 8371542
}
```


Fig. 7.3 Sample of JSON File Response for Confirming an Account Permissioned Control

– **Step 2:** CHAIN ADMIN, who are the only users, can sell products on the marketplace and their activities are supervised by the MASTER ADMIN users. Figure 7.4 shows one of the CHAIN ADMIN accounts and the products listed in the marketplace.

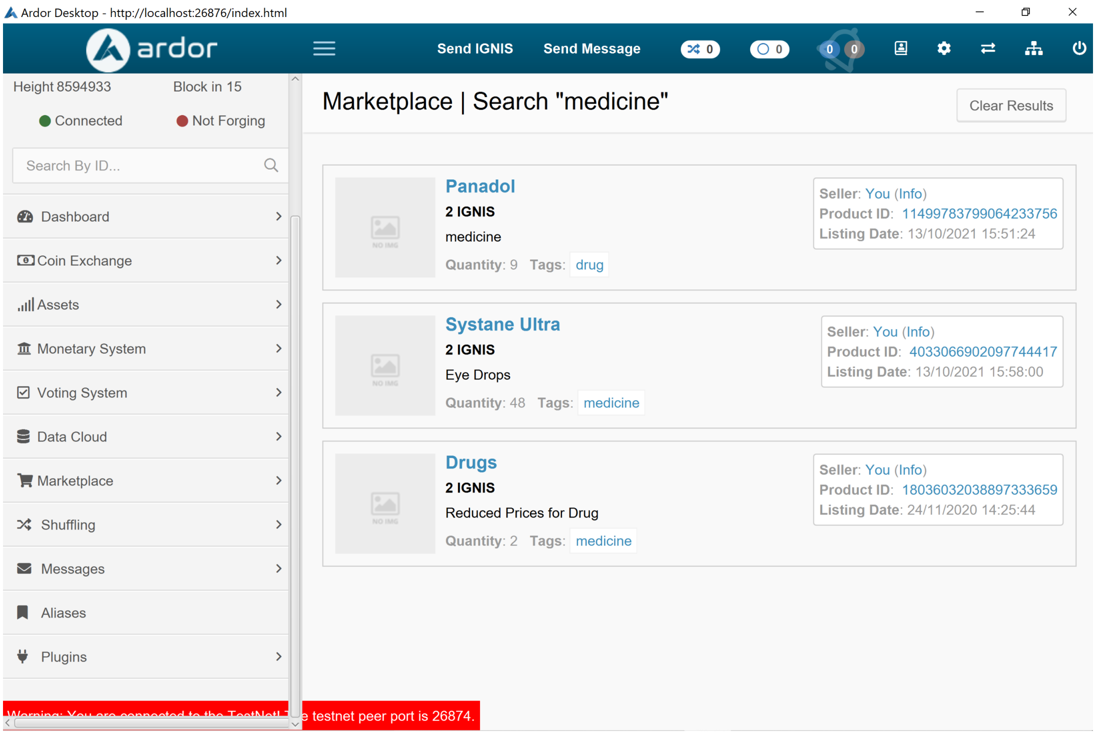


Fig. 7.4 Sample of a CHAIN ADMIN Account with a List of Products to be Listed on the Marketplace

– **Step 3:** once the CHAIN ADMIN has received an alert that is checking for nearly expired drugs (as described in Chapter 5), a predictive optimal price model is applied to the product which is about to expire to generate the optimal selling price.

– **Step 4:** the product is now ready to be displayed on the marketplace, as shown in Figure 7.5.

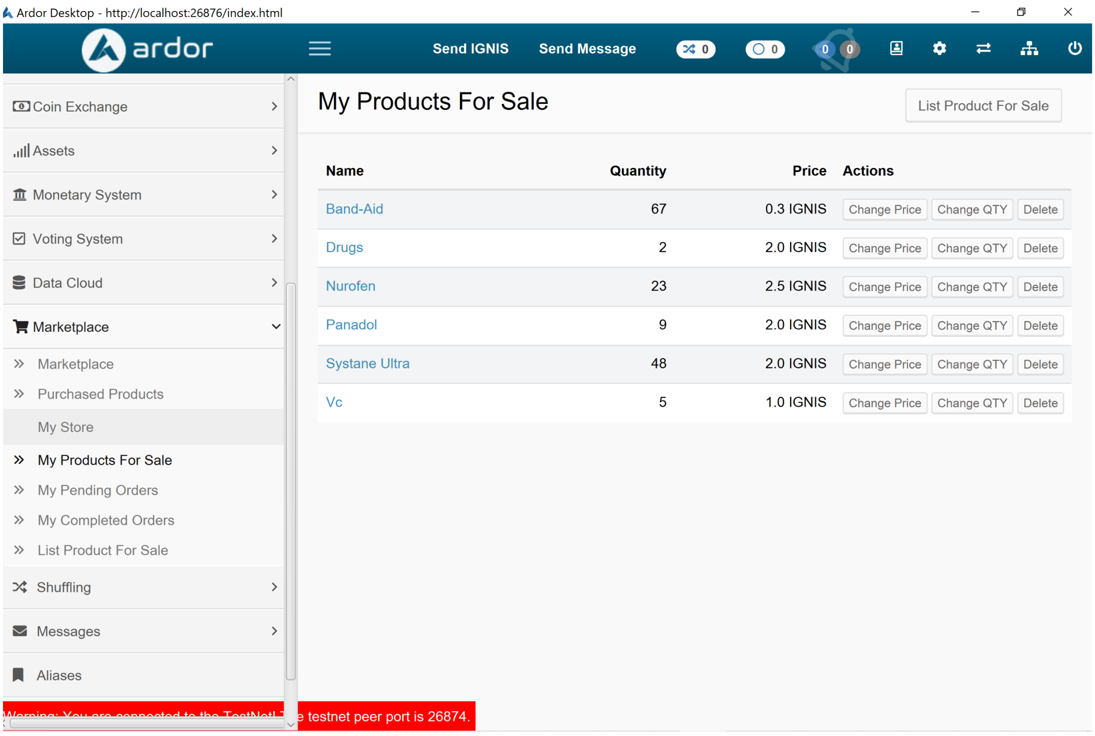


Fig. 7.5 Sample of a CHAIN ADMIN Account with Products Listed on the Marketplace

– **Step 5:** all digital items in the marketplace are listed in date order, showing the newest entry first. Every product has a Name, Price, Description, as well as a Seller account and a product id. Optionally, a product might also have a tag, which is keyword(s) to help describe what kind of product is being listed. Figures 7.6 and 7.7 display the product details listed in the marketplace and a confirmed transaction and a block generated in the blockchain for the listed product, respectively.

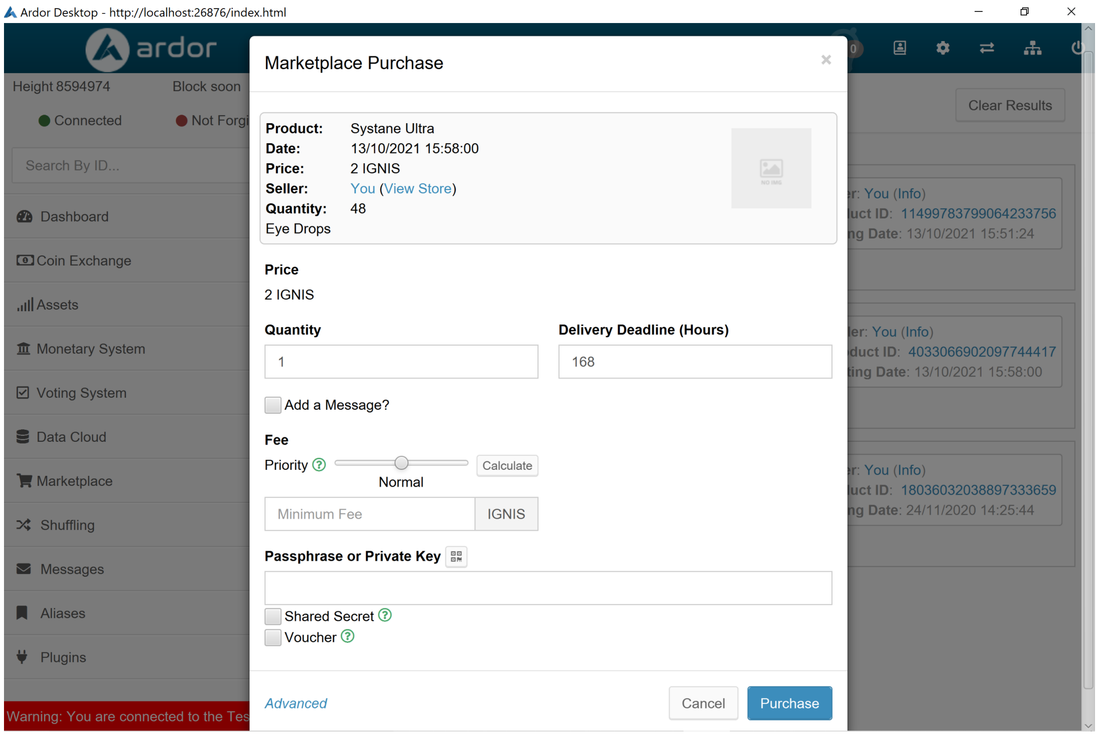


Fig. 7.6 Screenshot of a Product Listed on the Marketplace

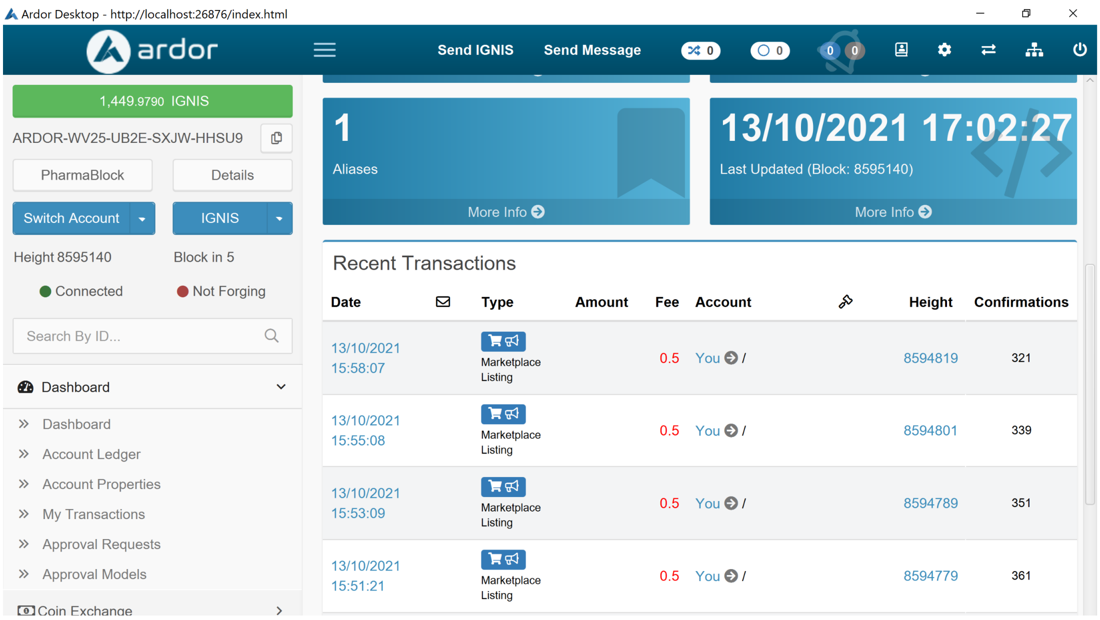


Fig. 7.7 Screenshot of Block generated on the Blockchain for a Listed Product

7.5 Dataset Used for Validation

The dataset used for validation is publicly available. We used a real-world dataset called the National Average Drug Acquisition Cost (NADAC) for the implementation [99]. This dataset was taken from an official platform of the United States government called *HealthData.gov* which offers a huge repository of health published data. The data set can be accessed from *https://healthdata.gov/dataset/NADAC-National-Average-Drug-Acquisition-Cost-2021/*.

Before making use of the dataset obtained from *HealthData.gov*, we modified some of the columns to fit our requirements. However, this modification was done without changing any of the drug prices or any important values. In particular, we changed the expiry date format from days to weeks. The reason for doing this was to allow the machine learning to deal effectively with the date values. Figure 7.8 shows the columns of the used dataset.

drugName	condition	rating	date	usefulCount	price	Discound pe...	discound Pri...	alarm date
Mirtazapine	Depression	10	Feb 28, 2012	22	14	0.200	11.200	Sep 1, 2011
Mesalamine	Crohn's Dise...	8	May 17, 2009	17	65	0.200	52	Nov 18, 2008
Bactrim	Urinary Tract I...	9	Sep 29, 2017	3	87	0.200	69.600	Apr 2, 2017
Contrave	Weight Loss	9	Mar 5, 2017	35	34	0.200	27.200	Sep 6, 2016
Cyclafem 1 / 35	Birth Control	9	Oct 22, 2015	4	26	0.200	20.800	Apr 25, 2015
Zyclara	Keratosis	4	Jul 3, 2014	13	88	0.200	70.400	Jan 4, 2014
Copper	Birth Control	6	Jun 6, 2016	1	43	0.200	34.400	Dec 9, 2015
Amitriptyline	Migraine Prev...	9	Apr 21, 2009	32	12	0.200	9.600	Oct 23, 2008
Methadone	Opiate Withdr...	7	Oct 18, 2016	21	88	0.200	70.400	Apr 21, 2016
Levora	Birth Control	2	Apr 16, 2011	3	34	0.200	27.200	Oct 18, 2010
Paroxetine	Hot Flashes	1	Feb 22, 2017	17	23	0.200	18.400	Aug 26, 2016
Miconazole	Vaginal Yeast...	6	May 7, 2015	7	21	0.200	16.800	Nov 8, 2014
Belviq	Weight Loss	1	Sep 23, 2014	57	55	0.200	44	Mar 27, 2014
Seroquel	Schizoaffectiv...	10	Oct 8, 2014	19	51	0.200	40.800	Apr 11, 2014

Fig. 7.8 Screenshot of the Dataset Used for the Implementation of the Solutions

7.6 Working of the Prototype System

Our PharmaBlock marketplace platform carries out computations at two different levels, namely local computations and blockchain computations. In the blockchain level computations, all the drug information is stored in the blockchain and is also copied to the data cloud storage for Ardor child chain accessibility and utility. In the local level computations, all drug pricing is executed locally. However, in our proposed marketplace, the computations for the optimal selling price occurs locally. All steps for both computation levels are presented as follows in 6.6.1 and Section 6.6.2 respectively.

7.6.1 Steps in PharmaBlock Blockchain

First, the CHAIN ADMIN provides the platform using APIs to feed the data streams to PharmaBlock platform on the fly. The process of calculating the optimal selling point is illustrated in Figure 7.9 and described as follow:

- Step 1: PharmaBlock receives the data streams from the CHAIN ADMIN.
- Step 2: The drug information is stored and copied to Ardor Data Cloud Storage using smarts contracts.
- Step 3:A new block is generated and an optimal price is sent to the marketplace once the steps in the local devices have been performed.

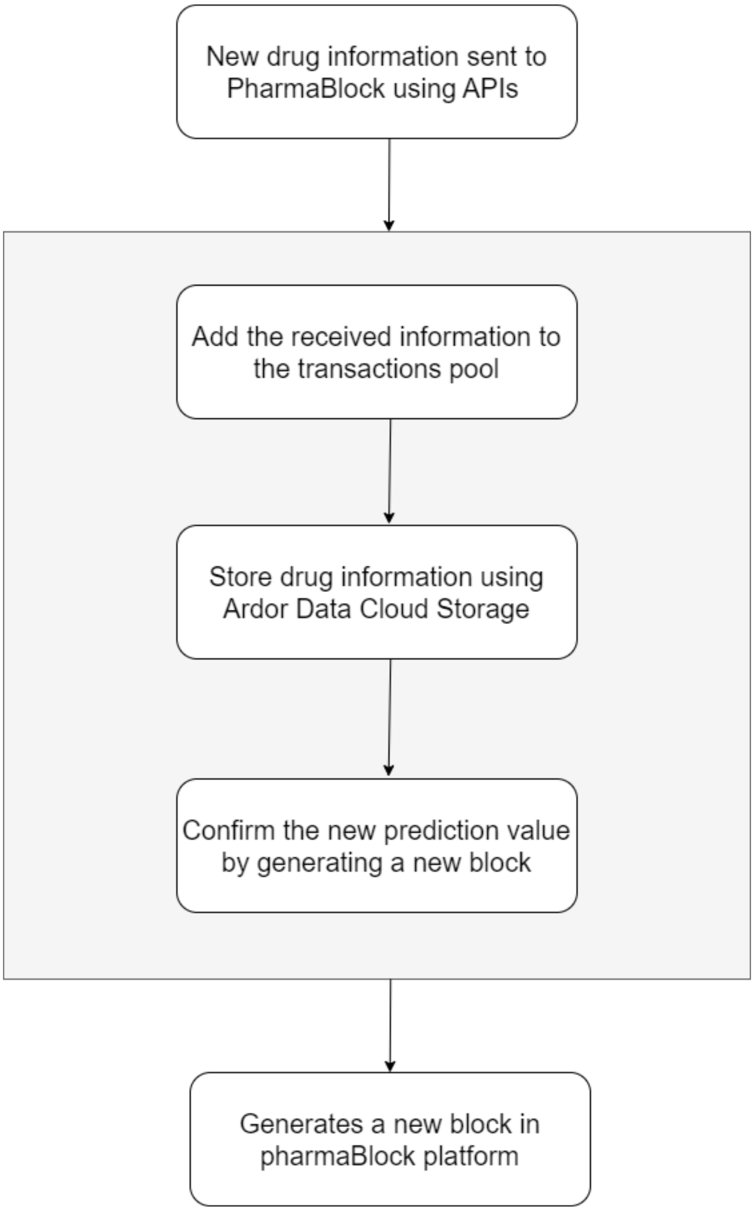


Fig. 7.9 Flowchart of PharmaBlock Computation Process

7.6.2 Steps in Local Devices

After extracting the drug information from PharmaBlock, we use this data in the local device to find the best selling price. The process of calculating the optimal selling point is illustrated in Figure 7.10 and described as follows:

- Step 1: Copy all the necessary information from PharmaBlock and store it in the local device.
- Step 2: Execute an optimal price algorithm in the local machine to predict the best price to sell the nearly expired drugs.
- Step 3: Results of the predicted prices are sent back to the PharmaBlock marketplace.

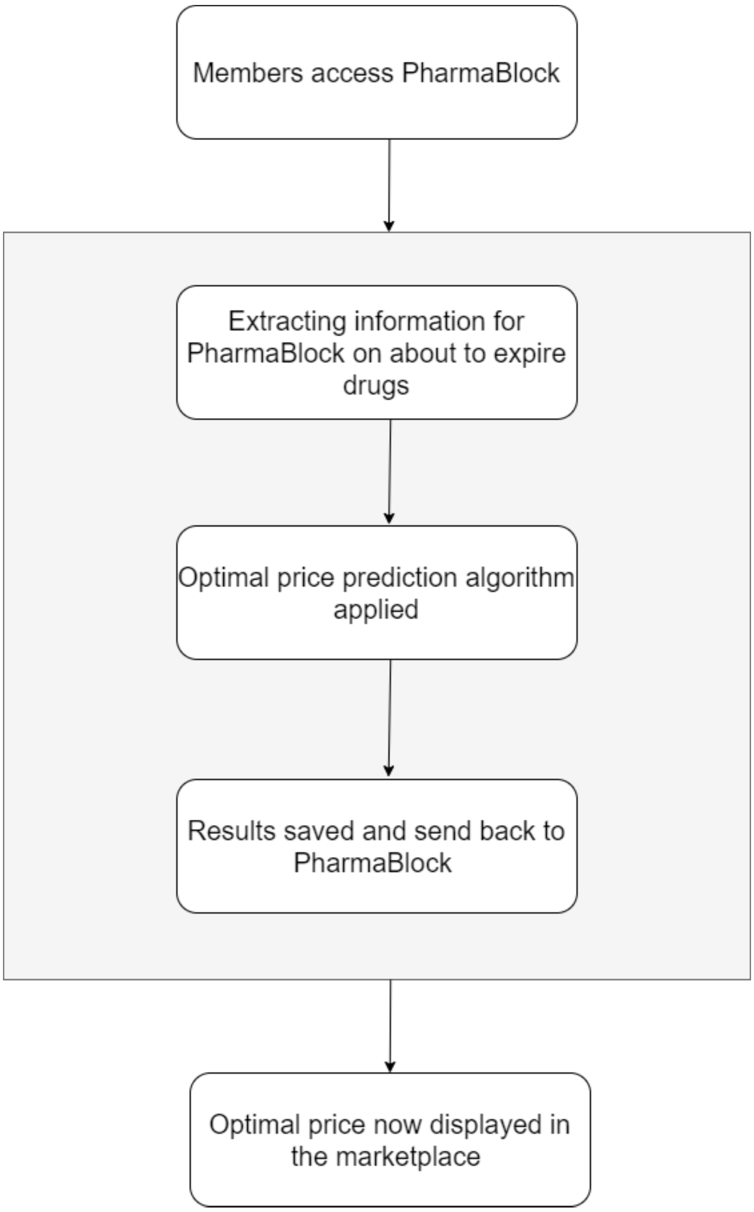


Fig. 7.10 Flowchart of Local Device Computation Process

7.7 System Evaluation, Results and Discussion

In this section, we present our mechanism for predicting the optimal selling price using Azure Machine Learning and the RapidMiner platform to generate the best price for drugs which are about to expire using supervised learning, as shown in Figure 7.11.

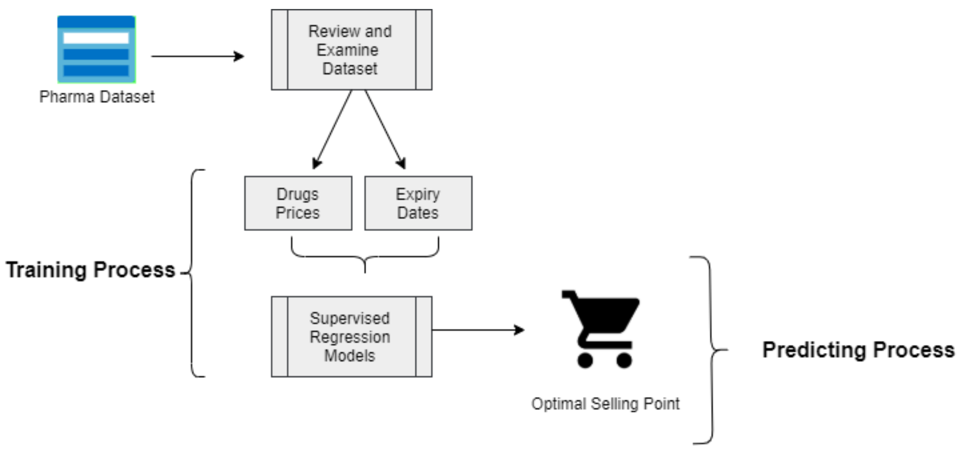


Fig. 7.11 The Experiment Framework for E-marketplace

Our model consists of the following three phases: Stage 1: preparing the dataset; Stage 2: the training process; Stage 3: the predicting process. First, the dataset comprises several columns namely, Drug-Name; Drug-Price; Expiry-Date and consists of about 780 records. Then, we examined the dataset manually to ensure the quality of the data. Second, we trained various supervised algorithms using the training dataset using Drug-Name, Drug-Price, and Expiry-Date as inputs. Third, we evaluated our models and examined their ability to predict.

In this experiment, we used two machine learning platforms - Azure ML Studio [98] and Rapid Miner Platform [88]. We evaluated and compared nine algorithms to predict the accuracy of the selling price for the drugs. The algorithms that we selected were not available on one platform; rather they were available across two different platforms. Hence, we selected the two platforms to use pre-packaged algorithms for our evaluation. Subsequently, the performance of the algorithms across the two platforms was evaluated using the benchmark (Root Mean Square Error).

7.7.1 Optimal Price Predictive Model Using Azure Machine Learning

1. ***Decision forest regression***

   The decision forest regression model performs a sequence of simple tests for each tree where the output of each tree makes a prediction until a decision is reached for all trees in the model. This model is widely used in the sale of products and pricing. This model has a huge number of applications, as described in [100]. In this study, we made use of the decision forest regression in Azure machine learning by dividing our dataset into two groups, 70% and 30% for training and testing, respectively. Visualizing the score and evaluating the models show how far the predictive values vary from the original price and we calculate the difference between these two values. Table 7.1 details the performance of this model.

Negative log likelihood	152.6
Mean Absolute Error	0.81
Root Mean Squared Error	1.2
Relative Absolute Error	0.059
Relative Squared Error	0.047
Coefficient of Determination	0.99

Table 7.1 Decision Forest Regression Model - Performance

2. ***Neural network regression***

   This type of regression can analyse complex problems and provide accurate answers. Training this type of regression will perform gradient descent to find the best coefficients to better fit the data [101]. Neural network regression is a supervised learning method dealing with numerical values, therefore it requires a labelled and numerical dataset. In this experiment, we used the neural network regression model to obtain the optimal regression coefficients and the optimal weight for the model. An evaluation of the model values shows how closely the data fits the model, with the coefficient of determination being 0.92 and the root mean squared error being 0.48. Table 7.2 shows the performance of this model.

Mean Absolute Error	0.33
Root Mean Squared Error	0.48
Relative Absolute Error	0.02
Relative Squared Error	0.007
Coefficient of Determination	0.92

Table 7.2 Neural Network Regression Model - Performance

3. ***Boosted Decision Tree Regression***

   This regression model uses boosting which means each tree is dependent on prior trees. This type of regression learns by fitting the remaining trees that preceded it, which helps to improve the accuracy of the model. The boosted decision tree builds a series of regression trees in a step-wise manner, using a predefined loss function to measure the error in each step and correct it in the next level [102]. The evaluation of this model shows an excellent coefficient of determination score of 0.97 and a mean absolute error of around 0.26. Table 7.3 provides the evaluation metrics of this model:

Mean Absolute Error	0.26
Root Mean Squared Error	0.98
Relative Absolute Error	0.02
Relative Squared Error	0.003
Coefficient of Determination	0.997

Table 7.3 Boosted Decision Tree Model - Performance

4. ***Bayesian Linear Regression***

   Bayesian linear regression uses linear regression supplemented by additional information in the form of combined prior parameter information to generate estimates for these parameters. This model does not find the single best value of the model parameters, it determines the posterior distribution for the model parameters. This algorithm is commonly used to predict the value of the dependent variable [103]. In this study, we made use of Bayesian linear regression to predict the value of the variable ''Discount-Price" for each drug. Analysing and evaluating machine learning after the training gives us an acceptable value of root mean squared error of 0.75. Table 7.4 lists the evaluation metrics for this model:

Negative log likelihood	405.1
Mean Absolute Error	0.055
Root Mean Squared Error	0.075
Relative Absolute Error	0.04
Relative Squared Error	0.01
Coefficient of Determination	1.0

Table 7.4 Bayesian Linear Regression Model - Performance

7.7.2 Optimal Price Predictive Model Using RapidMiner Machine Learning:

1. ***Generalized Linear Model Regression***

   The generalized linear model (GLM) differs from other models by its ability to test non-linear models in the context of regression. GLM is a mathematical framework and a supervised mechanism. This model is widely used because of its natural approximation for complex functional relationships and it is straightforward in terms of estimating unknown parameters [89]. In this study, we apply generalized linear regression to our dataset using the RapidMiner platform and the performance of this model is shown in Table 7.5. The expected output is a regression model that will predict the optimal selling point for nearly expired drugs.

Root Mean Squared Error	0.188 +/- 0.032 (micro average: 0.191 +/- 0.000)
Absolute Error	0.149 +/- 0.034 (micro average: 0.149 +/- 0.119)
Relative Error Lenient	1.14% +/- 0.60% (micro average: 1.15% +/- 2.84%)
Squared Error	0.036 +/- 0.012 (micro average: 0.036 +/- 0.054)
Correlation	1.000 +/- 0.000 (micro average: 1.000)

Table 7.5 Generalized Linear Regression Model - Performance

2. ***Deep Learning regression***

   The deep learning model is a deep neural network that is trained to extract features from a large group of examples to assign labels to textual units. It has been proven to be powerful in mimicking human skills. It has a wide range of applications such as those detailed in [91]. In this study, the deep learning algorithm is used for regression to build a mathematical equation to predict the optimal price to sell expired drugs in the marketplace and we designed and applied deep learning in RapidMiner to build the model. The performance metrics results of this model are shown in Table 7.7.

Table 7.6 Deep learning model - performance

Root Mean Squared Error	0.489 +/- 0.082 (micro average: 0.495 +/- 0.000)
Absolute Error	0.373 +/- 0.042 (micro average: 0.374 +/- 0.324)
Relative Error Lenient	2.95% +/- 2.19% (micro average: 2.97% +/- 7.29%)
Squared Error	0.245 +/- 0.081 (micro average: 0.245 +/- 0.469)
Correlation	1.000 +/- 0.000 (micro average: 1.000)

Table 7.7 Deep Learning Model - Performance

3. ***Decision Tree Regression***

   The decision tree model has a root at the top and grows downwards. This algorithm splits the dataset into segments and small branches, and all segments form the decision tree. Decision tree regression is used to predict the target variable whose values are continuous in nature. A regression tree can easily handle complicated data. This model has been widely used for data mining, as in [92]. In this paper, we use the decision tree algorithm to build a model to predict the best selling price depending on the available amount of drugs and their expiry date. We implement our model using the SVR operator on the RapidMiner Platform and the output is a regression model that will determine the discount. The performance metrics are shown in Table 7.8.

Root Mean Squared Error	0.380 +/- 0.072 (micro average: 0.382 +/- 0.000)
Absolute Error	0.294 +/- 0.039 (micro average: 0.298 +/- 0.320)
Relative Error Lenient	1.71% +/- 1.06% (micro average: 1.69% +/- 6.30%)
Squared Error	0.221 +/- 0.073 (micro average: 0.221 +/- 0.432)
Correlation	1.000 +/- 0.000 (micro average: 1.000)

Table 7.8 Decision Tree Model - Performance

4. ***Support Vector Regression***

   Support vector regression (SVR) uses the same principle as SVM, but for regression problems. This algorithm can be a regression model which performs well in different domains. It was developed in [93] for both binary classification and regression and it was applied successfully in many applications, such as those detailed in [94].]. In this study, the linear support vector regression algorithm is used for regression and we make use of the SVR model in RapidMiner to build our model. To train and test the SVR model, we divided the dataset into two classes, 70% and 30%, for training and testing respectively. The performance metrics are shown in Table 7.9.

Root Mean Squared Error	0.023 +/- 0.010 (micro average: 0.025 +/- 0.000)
Absolute Error	0.016 +/- 0.005 (micro average: 0.016 +/- 0.019)
Relative Error Lenient	0.31% +/- 0.53% (micro average: 0.32% +/- 1.66%)
Squared Error	0.001 +/- 0.001 (micro average: 0.001 +/- 0.002)
Correlation	1.000 +/- 0.000 (micro average: 1.000)

Table 7.9 Support Vector Model - Performance

7.7.3 Prototype Results and Discussion

We developed an on-the-fly intelligent and predictive analytical approach to predict an optimal price to sell products in a decentralized marketplace, as shown in Figure 7.11. The work develops intelligent decision making centred on the just-in-time sale of drugs at an optimal price to consumers on a decentralized marketplace platform. A summary of the predictive analytical approaches is given in sections 4 and 5 with an overview of several machine learning algorithms applied to our framework with a discussion on their performance. Additionally, to conduct supervised machine learning, we built our dataset using the RapidMiner platform and the Azure Machine Learning platform. We conducted a 2-fold cross-validation in this experiment, meaning the data is divided into two groups, one being the training set and the other being the test set. We used eight approaches to predict the optimal price for selling medicines on our PharmaBlock platform. To evaluate our model, we used well-known evaluation metrics, namely mean absolute error (MAE), root mean squared error (RMSE) , relative absolute error, relative squared error and coefficient of determination for each approach. Tables 7.1-7.9 detail the performance evaluation for each approach. RMSE and MAE are regularly employed in model evaluations and are two of the most popular metrics used to assess regression efficiency [104]. RMSE indicates how concentrated the data is around the regression line of best fit and a smaller RMSE indicates smaller forecast errors, meaning that our model scores the best values of between 0.023 – 1.2 for all the algorithms. We conducted the experiment and the results show that the support vector regression model achieves the best performance when using the RMSE metric over the other regression models, whereas the decision forest regression model has the worst performance.

In summary, the model trained on both platforms achieved a very accurate level of prediction and the results of this analysis show that more than 92% of the prices were predicted correctly in the PharmaBlock platform. Further, this work provides regression models that can determine the best price to sell drugs that are nearly expired using several approaches. In summary, this study is the first to provide a date-based early warning system in the pharmaceutical supply chain management area using blockchain technology which is supported by an intelligent predictive selling model based on the marketplace.

7.8 Validation of the Prototype System

To validate the proposed solution for this objective, we used the Azure machine learning studio to deploy our web services model. The web services create and prepare the code for the model and it will also develop a URL and API key to use the predictive model and to facilitate access for the developer. We download the Excel file for our Drug Price Predictive Model into a local device, as shown in Figure 7.12.

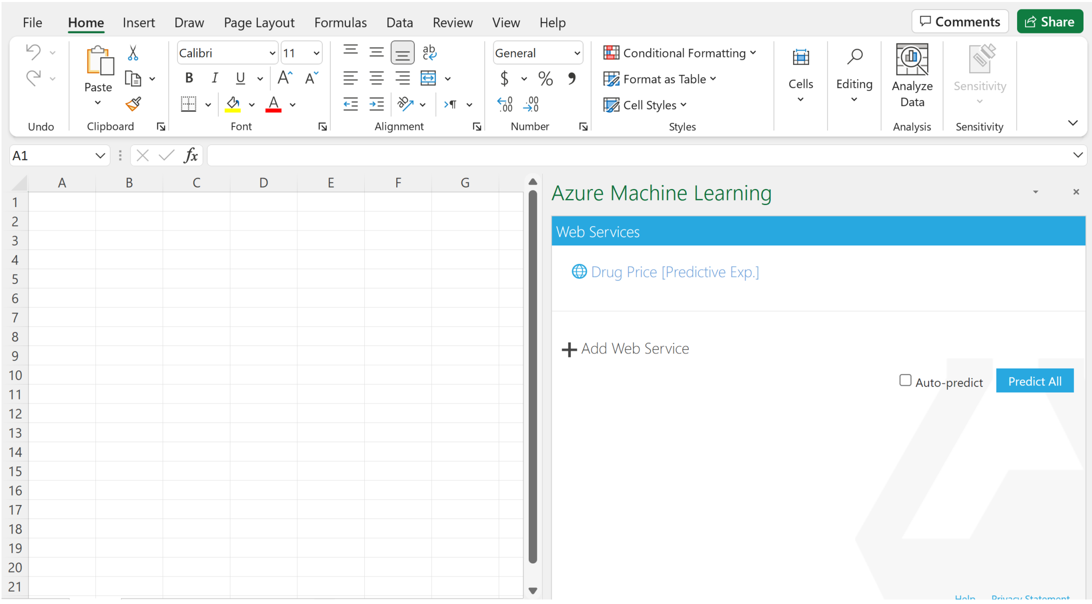


Fig. 7.12 A Screenshot of Drug Predictive Price Model in Excel

We selected four inputs to the Drugs Price Predictive Model which are: **DrugName, Price, DiscoundPrice, and AlarmDate**. We have chosen one output which is the **Score Label**, this score label is the prediction value of the drug discount price column as shown in Figure7.13.

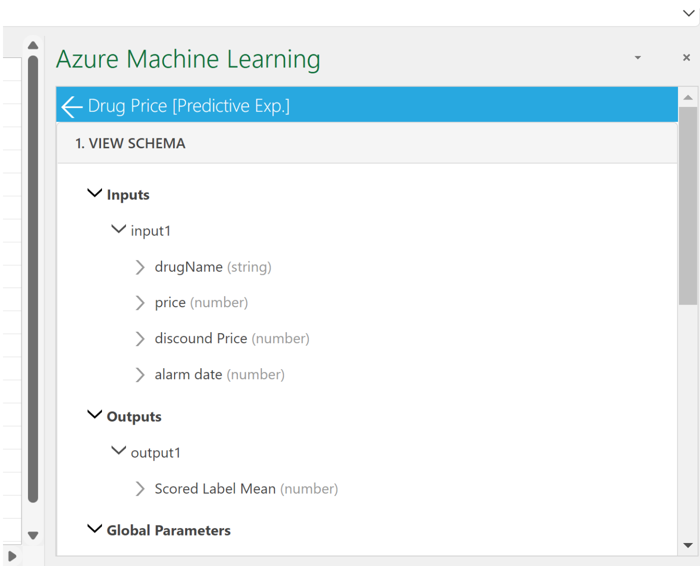


Fig. 7.13 A Screenshot of Output and Input Parameters in the Drug Predictive Price Model

We select a sample of our dataset that we used as shown in Figure 7.14 and Figure 7.15.

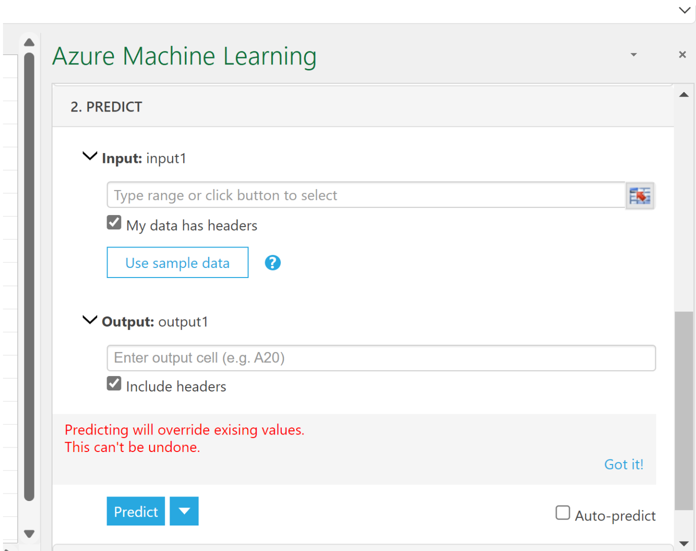


Fig. 7.14 A Screenshot of Sample Data Used

drugName	price	discound Price	alarm date
Mirtazapine	14	11.2	36
Mesalamine	65	52	47
Bactrim	87	69.6	14
Contrave	34	27.2	37
Cyclafem 1 / 35	26	20.8	17

Fig. 7.15 A Screenshot of Sample Data Used in Excel

Lastly, we asked the machine to predict the drug price using the intelligent predictive model and the result of the prediction are shown in Figure 7.16.

drugNam	price	discound	alarm da	Scored Labe
Mirtazapine	14	11.2	36	11.62335219
Mesalamine	65	52	47	50.68946429
Bactrim	87	69.6	14	69.21828808
Contrave	34	27.2	37	27.7
Cyclafem 1 /	26	20.8	17	20.76666667

Fig. 7.16 A Screenshot of the Output Prediction Values

7.9 Conclusion

In this chapter, we discussed all the phases that comprise the PharmaBlock marketplace framework to improve the strategies and increase the visibility of medicines in the pharmaceutical supply chain, reducing the number of counterfeit medications on the market and the wastage of expired drugs. In particular, we discussed in a step-wise manner the processes involved in extracting drug information from the ledger phase, the execution of the predictive machine learning model phase, and finally sending the optimal price to the marketplace phase. Additionally, we developed a price predictive model on both the Azure ML Studio and RapidMiner platforms and compared the results. We subsequently trained and compared eight prediction regression models and used those trained models on new nearly expiring medicines to predict the optimal price to sell them in the decentralized marketplace. This solution was developed to address the third research objective of this thesis.

In this chapter, we also proposed a simulation framework for validating the solution to research objective 3. This was done using a public and real dataset. At the end of the validation and implementation process, the results show that our proposal is able to generate and accurately send the optimal prices for the drugs.

The next chapter discusses in a methodological manner the steps involved in developing an intelligent predictive analytical method to compute the future drug demand requirements for manufactures.

Chapter 8

Predictive Model for Future Drug Demand

8.1 Introduction

In this chapter, the process of predicting a future drug demand-based framework is discussed. This chapter begins with a discussion of the phases of the prototype system workflow in creating the framework. Additionally, an intelligent model using machine learning predictive models is proposed to predict and compute the number of SKU drugs required to meet future demand. This proposed solution will help manufacturers produce the required amount of drugs, based on the number of previously wasted drugs in a certain area, taking into account population growth. This provides a complete solution to research objective 4. Also, this chapter presents the results of the implementation and validation of proposed solution to research question number four. We created an intelligent system that predicts the amount of the drugs needed to meet future demand based on the last period/s of drug demand based on multiple factors to answer this research question and we used the following to test the system:

1. **Blockchain:** is a distributed digital ledger that is used for recording transactions across different and multiple nodes [10]. For our purposes, we use a permissioned parent-child chain for storing the pharmaceutical supply chain data.

2. **Azure Machine Learning Studio:** is a cloud-based service designed to streamline and expedite the machine learning project life-cycle. It is used by professionals in the field, such as data scientists and engineers, to train and deploy models. [98].

The outline of this chapter is as follows. In Section 8.2, we outline the phases of the workflow of the Future Drug Demand Predictive Model. In Section 8.3, we describe our prototype system implementation and the aim of engineering this prototype. In section 8.4, we discuss our predictive future drug model and detail the design of the workflow to validate the proposed framework. In Section 8.5, we describe the dataset used for validation purposes. In Section 8.6, we explain in detail in a stepwise manner the detailed working of the system prototype. In Section 8.7, we discuss the results obtained from the evaluation. In section 8.8, we validate the prototype system framework. Finally, section 8.9 concludes this chapter.

8.2 Workflow of the Future Drug Demand Predictive Model in PharmaBlock

Globally, drug wastage is one of the challenges of pharmaceutical supply chain management. Many developing and low-income countries are suffering from the inaccessibility of medicines. Unwanted and expired medicines negatively affect a country's financial capability and also affects the environment [105].

In this section, we present the mechanism by which manufacturers can predict future drug demand and we also present the main purpose of using the intelligent predictive model which is to compute the future demand for drugs to reduce the amount of drug wastage every year. In our intelligent system, the predictive analytical model will intelligently compute the future demand for drugs. To achieve this goal, we used data from a large medicine manufacturer, and form the Intelligent Rule Engine as input such as the population number and then the provided data will be processed using the best performing predictive models. As the output, we aim to reduce the amount of wasted drugs by obtaining the optimal number of drugs to be produced to meet future demand, where the output is the value suggested to manufacturers for producing the number of drugs needed in the future which will be recorded as a block transaction in the blockchain for future statistics.

To achieve this goal, machine learning models are applied which are widely used in medical area for predicting future events. To develop a future demand prediction model for pharmaceutical manufacturers using machine learning algorithms, a real pharmacy dataset is used to achieve this goal. The process starts by dividing the dataset into four parts depending on seasonal sales. Then, we selected the features for the dataset. After that, three machine learning regression-based algorithms are selected and tested in the RapidMiner Studio Platform. Then, we determine the performance of each model using three evaluation matrices: RMSE, R2 score, and accuracy. Figure 8.1 illustrates the workflow of future drug demand predictive module in PharmaBlock.

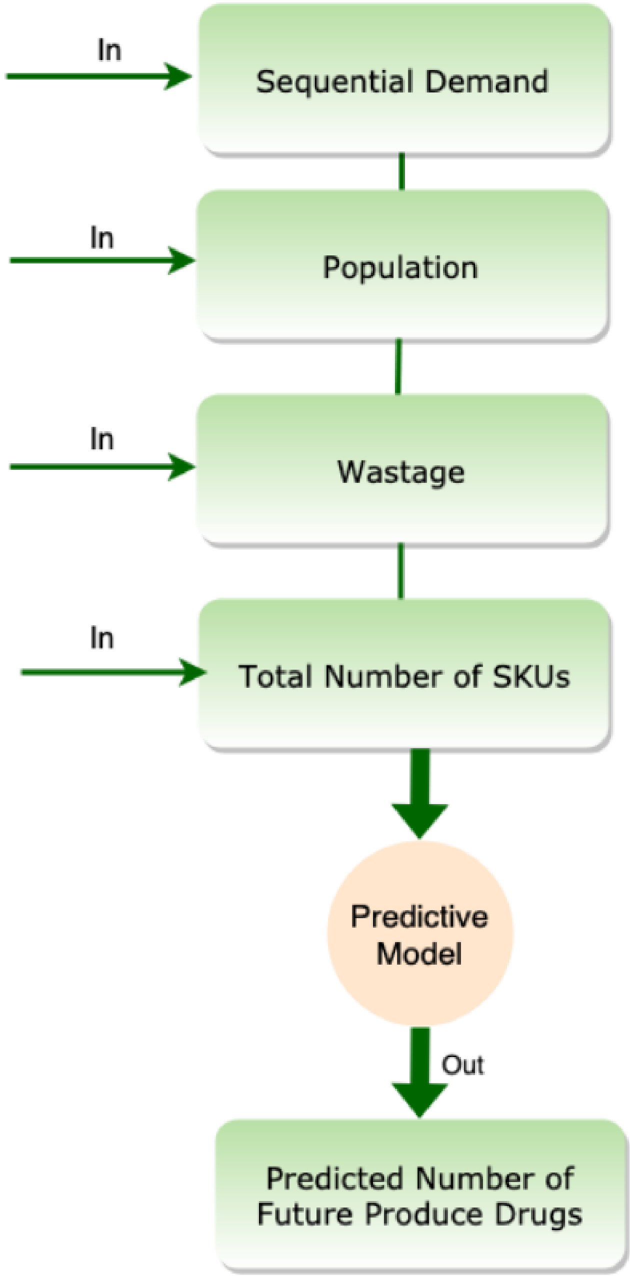


Fig. 8.1 Future Drug Demand Predictive Module.

8.2.1 Phase 1: Collect Information

In this phase, only those permissioned users who were assigned to the PharmaBlock platform as a CHAIN ADMIN (analyst) can collect and extract the required data from the data cloud storage in PharmaBlock. All the drug information needed has already been copied to the data cloud storage to analyse these data and apply the machine learning and predictive model. A CHAIN ADMIN can access the decentralized data storage on the Ardor platform to collect the data related to the production of the drugs, data related to the number of sales from pharmacies, and statistics related to the population in the area.

8.2.2 Phase 2: Execution of the Future Demand Predictive Model

After extracting all the drug information, the manufacturers need to determine the amount of drug wastage by applying a price predictive model. In this phase, the information from the data cloud storage is collected as a dataset and sent to the machine learning model to analyse the drug information to predict the future demand for drugs. This is to reduce the number of expired drugs which are discarded to reduce the negative impact on the environment.

8.2.3 Phase 3: Send Result to Drug Manufacturers

After using the predictive machine learning models, a block is generated to store the results in PharmaBlock which are then sent to the manufacturer to be analysed so future drug demand can be predicted. Figure 8.2 illustrates the working process of the previous three phases.

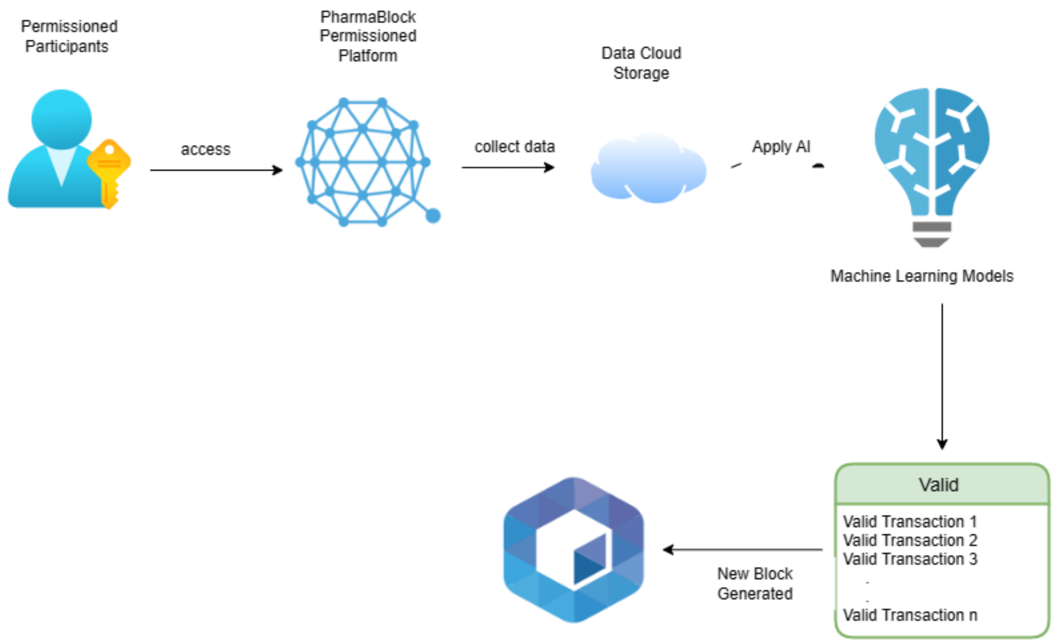


Fig. 8.2 Workflow of Future Demand in PharmaBlock.

8.3 Prototype System Implementation

The primary aim of engineering the prototype system is to simulate the working of the PharmaBlock Services, an intelligent framework that executes the future drug demand predictive model. Our objective is to use the developed PharmaBlock prototype to test the efficacy of the methods proposed in the previous section to enable manufacturers to benefit from the intelligent model by producing the required amount of drugs. As discussed in Chapter 2, in the current literature and also in practice, one of the major challenges of pharmaceutical supply chain systems is the waste of a large amount of expired drugs. With our intelligent framework which involves the integration of predictive models, manufacturers now can act effectively in relation to produced medicines. We used the Ardor blockchain technology as our computing platform and its programming language is Java. We also set up the environment using IntelliJ IDEA to run the Ardor server and deploy smart contracts. However, Ardor blockchain is in the development stage. Hence, it was not possible for us to use any other platform other than Ardor which supports child chaining.

8.4 Modeling and Designing the Future Drug Demand Prediction Model

This section details how we use the extracted statistics from PharmaBlock in Ardor and apply the intelligent predictive model to allow every permissioned manufacturer to increase or decrease drug production according to seasonality needs.

8.4.1 Workflow for the solution

This section details how we use the extracted statistics from PharmaBlock in Ardor and apply the intelligent predictive model to allow every permissioned manufacturer to increase or decrease drug production according to seasonality needs.

– **Step 1:** As mentioned before in Chapter 5, setting up the *The Child Chain Control* feature can give platform users the ability to control who can perform transactions on the child chain. In PharmaBlock, MASTER ADMIN nodes create databases and upload them using Ardor Data Cloud Storage such as: population statistics, the number of drugs wasted every year, the number of Stock Keeping Units (SKUs). Figure 8.3 shows the datasets in Data Cloud and Figure 8.4 shows the transaction details.

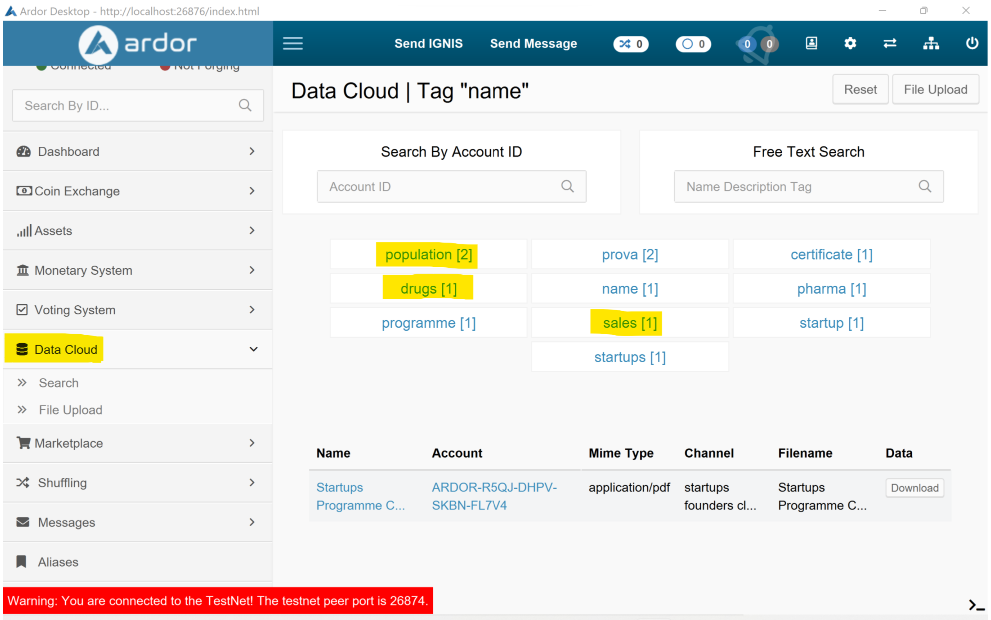


Fig. 8.3 Screenshot of the Data Cloud which Contains Different Files and Datasets

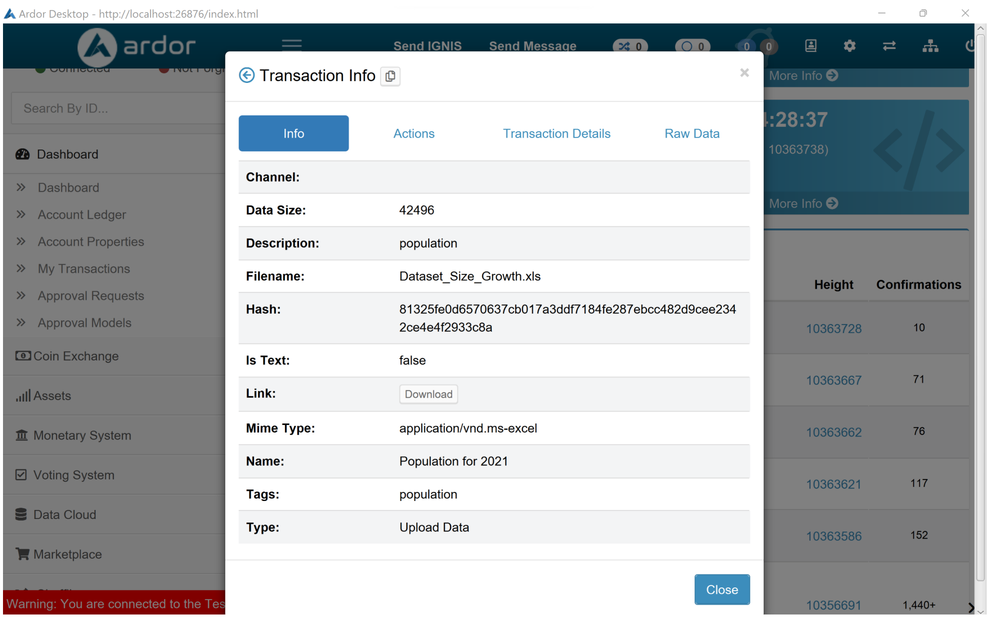


Fig. 8.4 Screenshot of the Data Transactions Uploaded to Data Cloud

– **Step 2:** Research Centres and Health Authorities which are MASTER ADMIN in PharmaBlock can use these uploaded datasets to analyse it and apply the intelligent predictive models to help in reducing drug wastage and improve the efficiency of PharmaBlock.

– **Step 3:** A block is generated for all the result outcomes from the previous step and every MASTER ADMIN and CHAIN ADMIN is informed.

8.5 Dataset Used for Validation

The dataset used for validation is publicly available. We used a dataset called Pharma sales data for the implementation [106].The data is real and built from an initial dataset comprising 600,000 transnational data collected over a period of 6 years (2014-2019), indicating the date and time of sale, pharmaceutical drug brand name and quantity sold, exported from the Point-of-Sale system in each pharmacy. This dataset was taken from **Kaggle**, an online platform for data scientists which is the world's largest data science community with powerful tools and resources.

Before making use of the dataset obtained from HealthData.gov, we modified some of the columns to fit our requirements but we did not change any of the drug sales or other important values. However, we changed the names of the drugs to their well-known commercial names. The reason for doing this was to allow the machine learning to deal effectively with the date values. Figure 8.5 shows sample rows and columns of the used dataset.

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Date	Panadol	Fevadol	Solpadeine	Paracetamol	Tylenol	Ultram	Brufen	Adol	Year	Month	Hour	Weekday Name
2	1/02/2014	0	3.67	3.4	32.4	7	0	0	2	2014	1	248	Thursday
3	1/03/2014	8	4	4.4	50.6	16	0	20	4	2014	1	276	Friday
4	1/04/2014	2	1	6.5	61.85	10	0	9	1	2014	1	276	Saturday
5	1/05/2014	4	3	7	41.1	8	0	3	0	2014	1	276	Sunday
6	1/06/2014	5	1	4.5	21.7	16	2	6	2	2014	1	276	Monday
7	1/07/2014	0	0	0	0	0	0	0	0	2014	1	276	Tuesday
8	1/08/2014	5.33	3	10.5	26.4	19	1	10	0	2014	1	276	Wednesday
9	1/09/2014	7	1.68	8	25	16	0	3	2	2014	1	276	Thursday
10	1/10/2014	5	2	2	53.3	15	2	0	2	2014	1	276	Friday
11	1/11/2014	5	4.34	10.4	52.3	14	0	1	0.2	2014	1	276	Saturday
12	1/12/2014	2	0.66	2.5	12	8	0	1	1	2014	1	276	Sunday
13	1/13/2014	7.34	7.66	6.2	52	9	0	7	1	2014	1	276	Monday
14	1/14/2014	6	1.33	12.3	33.7	6	1	0	2	2014	1	276	Tuesday
15	1/15/2014	4	2.34	5	26.7	12	2	3	3	2014	1	276	Wednesday
16	1/16/2014	6	2	4.3	28.3	19	1	5	0	2014	1	276	Thursday
17	1/17/2014	2	3.68	8.3	20.4	15	0	6	3	2014	1	276	Friday
18	1/18/2014	1	5.33	5.8	43.2	15	4	7	2	2014	1	276	Saturday
19	1/19/2014	4.33	4	4	14.1	4	0	1	1	2014	1	276	Sunday
20	1/20/2014	6	3.34	3.3	11.9	18	2	12	3	2014	1	276	Monday

Fig. 8.5 Screenshot Showing the Dataset Used for the Implementation of the Solutions

8.6 Working of the Prototype System

Our PharmaBlock platform carries out the computations at two different levels, namely local computations and blockchain computations. In the blockchain level computations, all the drug sales information is stored in the blockchain and is also copied to the data cloud storage for the Ardor child chains accessibility and utility. In the local level computations, all drug sales are executed locally. However, in our proposed future drug demand predictive computations, processing occurs locally. All steps for both computation levels are detailed in Section 8.6.1 and Section 8.6.2, respectively.

8.6.1 Steps in PharmaBlock Blockchain

The CHAIN ADMIN nodes provide the drug sales information using APIs to feed the data streams to the PharmaBlock platform on the fly. The process of predicting future drug demand in PharmaBlock is illustrated in Figure 8.6 and described as follows:

– Step 1: PharmaBlock receives the data streams by the CHAIN ADMIN nodes.

– Step 2: The drug sales information is stored and copied to Ardor data cloud storage using smarts contracts.

– Step 3: A new block is generated and a prediction of future drug demand is sent to the drug manufacturers once the steps in the local devices have been completed.

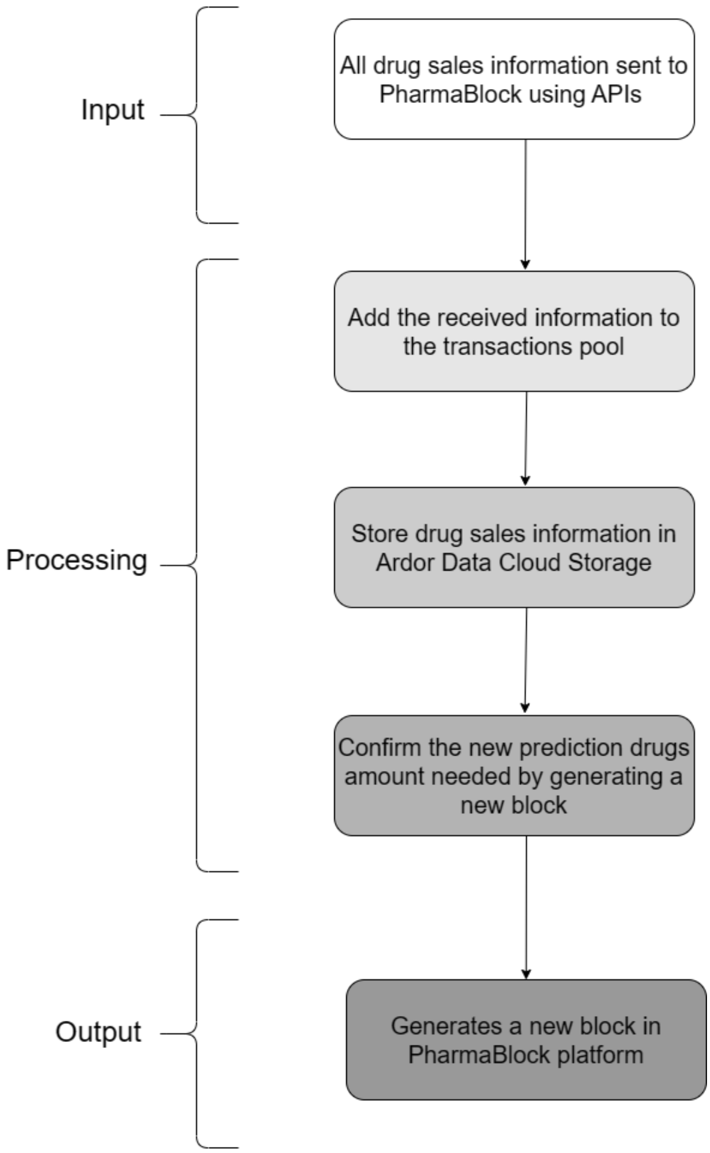


Fig. 8.6 Flowchart of PharmaBlock Computation Process

8.6.2 Steps in Local Devices

After extracting the drug sales information from PharmaBlock, we use this data in the local device to determine the future demand for a particular drug. The process of calculating the future demand for a drug is illustrated in Figure 8.7 and described as follows:

– Step 1: Copy all the necessary drug sales information from PharmaBlock data cloud storage and store it in the local device.

– Step 2: Execute the intelligent predictive algorithm in the local machine to predict the amount of each drug that will be needed.

– Step 3: Save the predictions in the PharmaBlock platform.

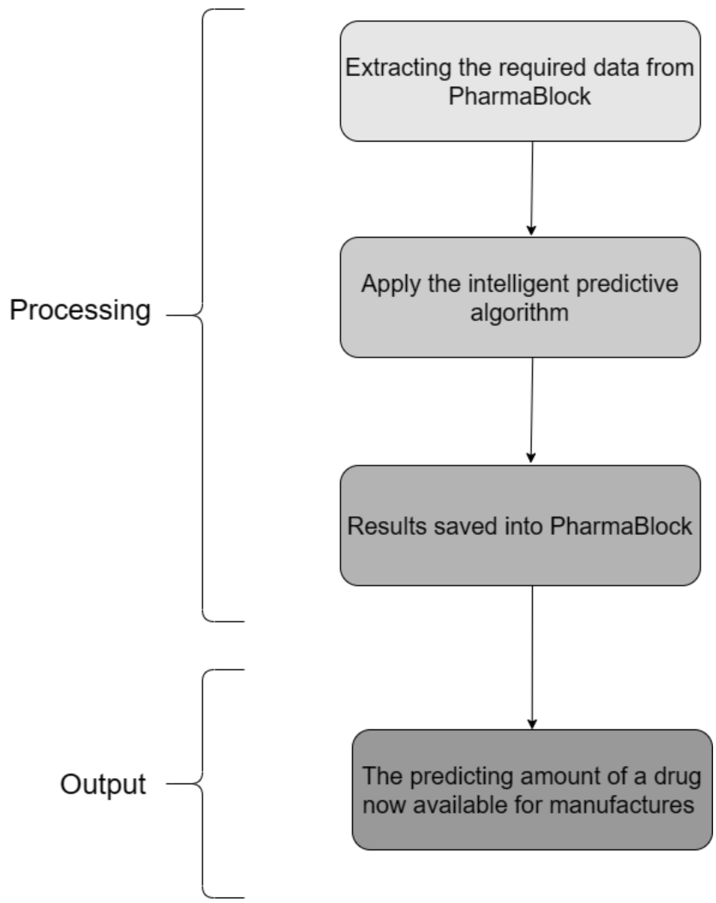


Fig. 8.7 Flowchart of Local Device Computation Process

8.7 System Evaluation, Results, and Discussion

In this section, we present our mechanism for predicting the future demand for drugs using the Azure Machine Learning platform and supervised learning as shown in Figure 8.8.

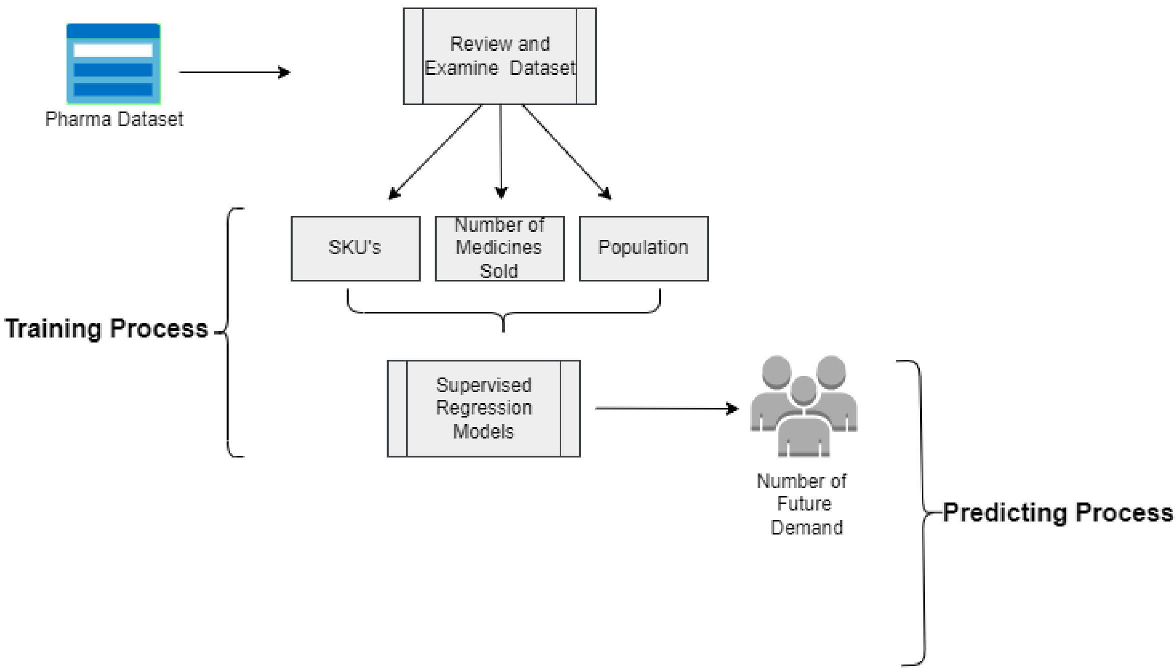


Fig. 8.8 The Experiment Framework for Drug Future Demand

Our model consists of three phases: Stage 1: preparing the dataset; Stage 2: the training process; Stage 3: the predicting process. The dataset comprises several columns namely, Date, Panadol, Fevado, Solpadeine, Paracetamol, Tylenol, Ultram, Brufen, Adol, Year, Month, Hour, and Weekday Name. The dataset consists of about 2099 records. We examined the dataset manually to ensure the quality of the data. Then, we trained various supervised algorithms using the training dataset and tested our models to evaluate their ability to predict future drug demand.

In this experiment, we applied the various supervised regression algorithms using Azure Machine Learning, to capture the best performance and results. Our model performance is detailed in the following section.

8.7.1 Future Drug Demand Predictive Model Using Azure Machine Learning

1. ***Decision forest regression***

   The decision forest regression model performs a sequence of simple tests for each tree where the output of each tree makes a prediction until a decision is reached for all trees in the model. This model is widely used in the sale of products and pricing. This model has a huge number of applications, as described in [100]. In this study, we made use of the decision forest regression in Azure Machine Learning by dividing our dataset into two groups, 70% and 30% for training and testing, respectively. Visualizing, the score and evaluate models show us how far the predictive values vary from the original price and calculate the difference between these two values. Table 8.1 details the performance of this model.

Negative log likelihood	698.8
Mean Absolute Error	0.77
Root Mean Squared Error	0.4
Relative Absolute Error	0.8
Relative Squared Error	0.3
Coefficient of Determination	0.71

Table 8.1 Decision forest regression model - performance

2. ***Neural network regression***

   This type of regression can analyse complex problems and provide accurate answers. Gradient descent is performed in this type of regression to find the best coefficients to better fit the data [101]. Neural network regression is a supervised learning method dealing with numerical values, therefore it requires a labelled and numerical dataset. In this experiment, we used the neural network regression model to obtain the optimal regression coefficients and the optimal weight for the model. An evaluation of the model values shows how closely the data fits the model, with the coefficient of determination being 0.92 and the root mean squared error being 0.65. Table 8.2 shows the performance of this model.

Mean Absolute Error	0.7
Root Mean Squared Error	0.65
Relative Absolute Error	0.5
Relative Squared Error	0.41
Coefficient of Determination	0.92

Table 8.2 Neural network regression model - performance

3. ***Boosted Decision Tree Regression***

   This regression model uses boosting which means each tree is dependent on prior trees. This type of regression learns by fitting the remaining trees that preceded it, which helps to improve the accuracy of the model. The boosted decision tree builds a series of regression trees in a step-wise manner, using a predefined loss function to measure the error in each step and correct it in the next level [102]. The evaluation of this model shows a good coefficient of determination score of 0.89 and a mean absolute error of around 0.54. Table 8.3 provides the evaluation metrics of this model:

Mean Absolute Error	0.54
Root Mean Squared Error	0.98
Relative Absolute Error	0.3
Relative Squared Error	0.09
Coefficient of Determination	0.98

Table 8.3 Boosted decision tree model - performance

4. ***Bayesian Linear Regression***

   This type of regression uses linear regression supplemented by additional information in the form of combined prior parameter information to generate estimates for these parameters. This model not only finds the single best value of the model parameters, it determines the posterior distribution for the model parameters. This algorithm is commonly used for predicting the value of the dependent variable [103]. In this study, we made use of Bayesian linear regression to predict the value of the variable "Drug quantity" for each drug. An analysis of the machine learning after the training gives us an acceptable root mean squared error of 0.9. Table 8.4 details the evaluation metrics for this model:

Negative log likelihood	498.1
Mean Absolute Error	0.7
Root Mean Squared Error	0.9
Relative Absolute Error	0.97
Relative Squared Error	0.93
Coefficient of Determination	0.33

Table 8.4 Bayesian linear regression model - performance

8.7.2 Prototype Results and Discussion

We developed an on-the-fly intelligent and predictive analytical approach to predict the future demand for drugs. A summary of the predictive analytical approaches is given in sections 8.4, 8.5 and 8.6 with an overview of the performance of several machine learning algorithms which were applied to our framework. Additionally, to conduct supervised machine learning, we built our dataset using the Azure Machine Learning platform. We conducted a 2-fold cross-validation in this experiment, meaning the data is divided into two groups, one being the training set and the other being the test set. We used four approaches to predict the future demand for drugs on our PharmaBlock platform. To evaluate our model, we used well-known evaluation metrics, namely mean absolute error (MAE), root mean squared error (RMSE), relative absolute error, relative squared error and coefficient of determination for each approach. Tables 8.1-8.4 detail the performance evaluation for each approach. RMSE and MAE are regularly employed in model evaluations and are two of the most popular metrics used to assess regression efficiency [104].RMSE indicates how concentrated the data is around the regression line of best fit and a smaller RMSE indicates smaller forecast errors, meaning that our model scores acceptable values of between 0.4 – 0.98 for all approaches. We conducted the experiment and the results show that the decision forest regression model achieves the best performance when using the RMSE metric over the other regression models, whereas the boosted decision tree regression model has the worst performance.

In summary, the model trained on the Azure ML platform achieved a very accurate level of prediction and the results of this analysis show that more than 86% of the future demand for drugs was predicted correctly in the PharmaBlock platform. Furthermore, this work provides regression models that can determine the demand for drugs using several approaches.

8.8 Validation of the Prototype System

To validate the proposed solution for this objective, we used the Azure Machine Learning Studio to deploy our web services model. The web services create and prepare the code for the model and it will also develop a URL and API key to use the predictive model and to enable the developer to access it. We downloaded the Excel file for our Future Drug Demand Predictive Model into a local device, as shown in Figure 8.9.

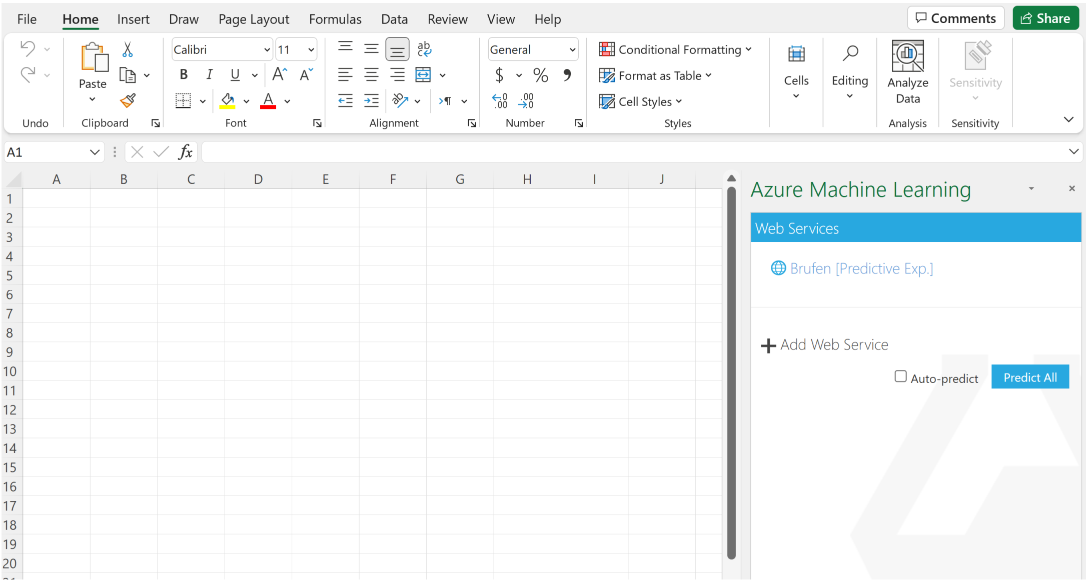


Fig. 8.9 A Screenshot of Drug Future Demand Model in Excel

We selected the following inputs for the Future Drug Demand Predictive Model: **Population, DrugWastage, SKU's, and DrugName**. We have chosen one output which is the **Score Label**, which is the predicted value of the drug discount price column, as shown in Figure 8.10.

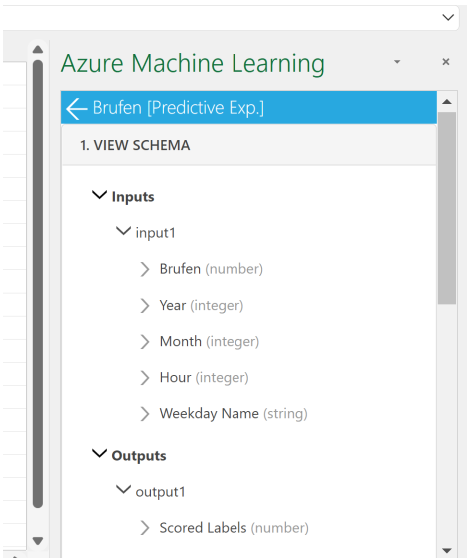


Fig. 8.10 A Screenshot of Output and Input Parameters in Drug Predictive Price Model

We select a sample of our dataset that we used as shown in Figure 8.11.

Brufen	Year	Month	Hour	Weekday
0	2014	1	248	Thursday
20	2014	1	276	Friday
9	2014	1	276	Saturday
3	2014	1	276	Sunday
6	2014	1	276	Monday

Fig. 8.11 A Screenshot of Sample Data Used

Lastly, we asked the machine to predict the drug price using the intelligent predictive model and the result of the prediction are shown in Figure 8.12.

Brufen	Year	Month	Hour	Weekday	Scored I
0	2014	1	248	Thursday	0.857813
20	2014	1	276	Friday	0.246088
9	2014	1	276	Saturday	1.301773
3	2014	1	276	Sunday	0.329123
6	2014	1	276	Monday	1.192416

Fig. 8.12 A Screenshot of the Output Prediction Values

8.9 Conclusion

In this chapter, we discussed all the phases that comprise the PharmaBlock framework to improve the strategies and increase the visibility of medicines in the pharmaceutical supply chain, reducing the number of counterfeit medications on the market and the wastage of expired drugs. In particular, we discussed in a step-wise manner the processes involved in extracting the drug sales information from the ledger phase, the execution of the predictive machine learning model phase, and finally predicting the amount of drugs needed to meet future demand. Additionally, we developed a predictive model on the Azure ML Studio platform and compared the results. We subsequently trained and compared four prediction regression models and used these trained models on drug datasets to predict the future demand for those drugs. This solution was developed to address the fourth research objective of this thesis.

In this chapter, we also proposed a simulation framework to validate the solution to research objective 4. This was done using a public and real dataset. At the end of the validation and implementation process, the results show that our proposed model is able to predict and send the results accurately to PharmaBlock platform.

The next chapter concludes the thesis and suggests possible directions for future research work.

Chapter 9

Conclusion and Future Work

9.1 Introduction

In this concluding chapter, we summarize the contributions that this thesis has made based on the objectives stated in Chapter 3 and we present an overview of the research results. We also discuss the important directions for future work that could be undertaken in this area of research. Many researchers have adopted blockchain technology in the area of pharmaceutical supply chains, but this research represents a pioneering effort in using artificial intelligence algorithms and smart contracts for blockchain. The research gaps were identified based on the outcome of our systematic literature review in Chapter 2, and this research has proposed a novel solution called PharmaBlock framework- based blockchain to address all the identified gaps.

9.2 Problems Addressed in this Thesis

The main objective of this thesis is to highlight the critical gaps related to the pharmaceutical supply chain based-blockchain in the existing literature. Based on the literature review in Chapter 2, the research issues that were identified and addressed in the thesis are as follows:

1. None of the existing literature uses any artificial intelligence techniques to classify stored data to enhance security and to enhance user privacy.

2. None of the existing literature has a personalised early warning system to detect and push about-to-expire drugs to the marketplace. None of the existing studies takes into account how pharmacies can benefit by the establishment of a decentralized marketplace for selling and purchasing nearly expired drugs using blockchain technology.

3. None of the existing literature takes into account how consumers can benefit from the establishment of a decentralized marketplace for selling and purchasing nearly expired drugs using blockchain technology and predicting an optimal selling price for drugs.

4. None of the existing literature uses artificial intelligence techniques to automatically predict the future demand for drugs based on historical data.

9.3 Summary of Thesis Contributions

This research added value to the data that is stored in the blockchain by creating an opportunity for consumers by setting up a platform for the decentralized marketplace for purchasing drugs in blockchain using a predictive model. From the pharmaceutical entities' perspective, this is the first study to provide a way by which stakeholders can access data over a blockchain and use this data in a respective field, such as research and drug quality management. Applying intelligent mechanisms to store data on a distributed platform will increase and enhance the user's trust in using and joining a pharmaceutical supply chain.

In this section, we present a summary of the thesis contributions. The major contribution of this thesis to the existing body of literature is to develop and evaluate a methodology for an intelligent pharmaceutical supply-chain-based blockchain. Before developing the complete solution for the proposed PharmaBlock framework, this thesis presents a systematic literature review of the various proposed approaches in the existing body of literature for pharmaceutical supply- chain-based blockchain. The following sections gives a brief overview of the research contributions.

9.3.1 Systematic Literature Review

In Chapter 2 of this thesis, we presented an extensive and systematic review of the existing literature in the areas of pharmaceutical supply-chain-based blockchain. To apply the process for the SLR, specific search terms were used in the following well-known databases:

- ACM Digital Library (www.dl.acm.org)
- MDPI Open Source (www.mdpi.com)
- IEEE Xplore (www.ieexplore.ieee.org/Xplore)
- Elsevier ScienceDirect (www.sciencedirect.com)
- SpringerLink (www.link.springer.com)
- ResearchGate (www.researchgate.net)
- Google Scholar (www.scholar.google.com.au)

The returned search results were subjected to inclusion and exclusion criteria and were evaluated for relevance. At the end of the evaluation process, 20 relevant papers were identified and critically reviewed. For the purpose of discussion and evaluation, we classified the existing research approaches into three classes based on the type of pharmaceutical supply chain as follows:

- Cold pharmaceutical supply chain
- Non-cold pharmaceutical supply chain
- Governance Pharmaceutical Supply Chain

At the time of writing this thesis, a journal paper which details the systematic literature review has been accepted by the International Journal of Grid and Web Services and is currently under review.

9.3.2 Creation of a Novel Solution: The PharmaBlock Framework

This thesis proposed and developed an intelligent platform for a pharmaceutical supply chain framework called PharmaBlock as a platform service. The framework can execute an intelligent model for data classification to model a secure intelligent information collection and classification process to increase the security of pharmaceutical information by allowing different levels of accessibility. This can also help researchers, large manufacturers, the FDA, and other stakeholders to assess and manage certain activities inside the blockchain. To do this, we proposed the use of PharmaBlock which intelligently stores pharmaceutical data. Additionally, our PharmaBlock framework is able to intelligently alert pharmacists when drugs are about to expire using a date-based early warning system. The framework can also execute an intelligent optimal selling point model-based marketplace to sell drugs at an optimal price. Lastly, PharmaBlock can predict future drug demand using an intelligent predictive approach. The intelligence that has been built into PharmaBlock provides reliable mechanisms that ensure the following:

9.3.2.1 Modelling an intelligent framework that generates personalized alerts for pharmacy retailers

We developed an intelligent mechanism using the Ardor network that generates personalized alerts on the PharmaBlock platform. This alert system is part of the artificial intelligence layer in the PharmaBlock framework and derives insights based on the underlying data stored in PharmaBlock. An algorithm to generate the date-based alerts based on the personalized value stored on the system is developed and tested.

9.3.2.2 Modelling an intelligent approach to predict the optimal selling point for drugs that are about to expire

We designed a decentralized marketplace platform-based blockchain using smart contracts and intelligent just-in-time decision making to predict the optimal price for selling about-to-expire drugs to other consumers. The marketplace uses intelligent decision making to provide recommendations on the optimal price to sell the drugs. A price predictive module is used to calculate the optimal selling price.

9.3.2.3 Modelling an intelligent approach that helps manufacturers to predict future demand for drugs

We developed an intelligent predictive analytical and reliable method to compute the future drug demand requirements for manufacturers, based on the previous years' consumption, taking into account the yearly population growth and the percentage of previously wasted drugs which is recorded in the blockchain. This model can predict and compute the number of SKU drugs required to meet future demand using machine learning predictive models to help manufacturers produce the amount of drugs required to meet demand.

9.3.3 Evaluation, Validation, and Implementation of the proposed solutions

To evaluate the performance and accuracy of the framework proposed in this thesis, we implemented it as a software prototype and tested the effectiveness of the proposed methods using the Ardor network. The working of the proposed prototype and the working of the developed prototype corresponding to each objective are detailed in Chapters 5-8.

9.4 Future Work

This study has undertaken research on using blockchain in a pharmaceutical supply chain, however, there are other issues that can be explored in the future. Our future work will explore the following avenues:

1. Research translation: Implementing the PharmaBlock framework in a real marketplace. In this research, we developed the PharmaBlock framework, conceptualized it and built a prototype of it. In future, this can be made into a commercial reality by building a commercial system that uses the PharmaBlock framework.

2. Automated ML for all aims, also referred to as AutoML, is the process of automating the time-consuming, iterative tasks of machine learning model development. It allows us to build ML models with high scale, efficiency, and productivity while maintaining model quality. In future work, PharmaBlock can be automated by applying machine learning end-to-end to address all aims and it additionally offers the advantages of generating simpler solutions and is faster to create.

3. Data classification and visual mechanism in PharmaBlock: the concepts of data classification, data mapping and data management have been well

defined in this thesis. As a part of future work, we will define more mature and detailed representations of these concepts, integrate them into more complex and secure blockchain networks and deploy them on a public network.

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